Radiotherapy, Utilizing Volumetric Modulated Arc Therapy, for Extensive Skin Field Cancerization: A Retrospective Case Series Assessing Efficacy, Safety, and Cosmetic Outcomes at 12 Months After Treatment

Lynda Spelman¹, b  David Christie⁰  Art Kaminski⁴  Christopher Baker⁵  Madeleine Supranowicz⁶  Robert Sinclair⁶

¹Specialist Connect Services, Brisbane, QLD, Australia; ²Queensland Institute of Dermatology, Brisbane, QLD, Australia; ³GenesisCare, Gold Coast, QLD, Australia; ⁴GenesisCare, Brisbane, QLD, Australia; ⁵St Vincent’s Hospital, Melbourne, VIC, Australia

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Abstract
Extensive Skin Field Cancerization (ESFC) describes multiple actinic keratoses, with and without keratinocyte skin cancers. These areas are characterised by dysplastic keratoses, are prone to new malignancies, involve significant morbidity, have a poor cosmetic appearance, and impact negatively on quality of life. Available topical field therapies have limited durability of efficacy. Volumetric modulated arc therapy (VMAT) is an advanced form of intensity-modulated radiotherapy which achieves highly modulated and conformal dosimetry, delivering a homogeneous dose, particularly over curved surfaces, for example, scalps and limbs. This series describes the 12-month follow-up analysis of 41 VMAT treated fields from 32 (21 M, 11 F) patients. Consent was obtained after VMAT treatment to allow access to outcomes data. Conditions treated include ESFC, Bowen’s disease/SCC in situ, cutaneous squamous cell carcinoma, and basal cell carcinoma (BCC). Efficacy was measured by the percentage reduction of visible pathology within the treatment field. The primary endpoint for this review was the assessment of treatment success, defined as >90% clearance of the treatment field. As part of this definition, the appearance of isolated keratoses at 12 months was considered not significant if the field overall was clear. The development of new or recurrent cancers within the 12-month follow-up period was recorded. Thirty-six fields (87%) achieved a clinical clearance >90%. Of
those, 33 (80%) fields achieved complete clearance >99% of visible actinic keratosis or keratinocyte cancers. Three fields (7%) demonstrated 91–99% clinical clearance, and no treatment failures were recorded. Two newly occurring lesions (1 BCC and 1 SCC in situ) were identified within a treated field at 12 months. The reported toxicities at 12-month post-treatment were grade 1 or 2 only, with no cases of persistent radiation dermatitis. Toxicities reported in more than 5% of cases included: alopecia (n = 4); dryness (n = 3); erythema (n = 2); and telangiectasia ulceration (n = 4). The high rate of complete clearance at 12 months seen in this case series compares very favourably with other treatments, including topical 5-fluorouracil, imiquimod, and photodynamic therapy. Toxicities reported in our patient population demonstrated that VMAT was well tolerated at 12-month post-treatment. VMAT treatment may play a growing role in future therapy for ESFC with and without keratinocyte cancers.

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Introduction

Extensive Skin Field Cancerization (ESFC) describes areas of solar damage involving multiple actinic keratoses, the clinical signs of photoaging, and variable numbers and types of keratinocyte skin cancers [1]. These areas are prone to new malignancies, including melanoma and non-melanoma skin cancer [1]. Significant morbidity is associated with the condition including discomfort, pruritus, and scaling, along with a poor cosmetic appearance. As a result, psychosocial impairment and isolation are reported by many patients, impacting negatively on their quality of life [2].

Ongoing and extensive surgical treatment may be required for many patients, which can be poorly tolerated in the elderly and those with multiple comorbidities. Patients may also decline surgery because of the fear of poor functional or cosmetic outcomes, or simply from a surgical weariness associated with high tumour loads. Furthermore, current topical field therapies that are generally used as a first-line treatment approach for ESFC, have demonstrated limited durability outcomes with both frequent recurrence and short-term cancer prophylaxis [1, 3].

Advances in radiotherapy techniques over the past 3 decades have allowed for highly modulated and conformal dosimetry delivering a more homogeneous dose throughout the field and better containment within the field. This avoids areas of over dosing (hot spots) or under dosing (cold spots) hence, reducing the risks of scarring and cancer recurrence [4]. These incremental improvements in radiotherapy techniques have been applied across a broad range of tumour types, including ESFC [5, 6]. Existing studies have involved problematic tumours of the head and neck, especially the nose, scalp, and perioral regions [7–9]. Adoption of radiotherapy for ESFC at other sites has followed naturally, as the technological expertise and capability has improved [6, 9]. The most recent iteration of these radiotherapy techniques is volumetric modulated arc therapy (VMAT) that offers shorter treatment times and greater regional flexibility compared to preceding techniques.

Methods

The outcomes in this series are derived from the National Dermatology Radiation Oncology Registry (NDROR) that collects and collates patient demographics, medical history, and treatment data for patients undergoing radiotherapy for ESFC, skin cancer, and inflammatory
skin conditions. Patient enrolment and consent was obtained consecutively, and permitted at 2 times points which included: (a) prospective consent prior or during the commencement of treatment; and (b) retrospective consent obtained after completion of treatment with patient permission granted to access data pertaining to their treatment.

This case series evaluates data for those patients who consented retrospectively having been clinically or biopsy diagnosed and treated for ESFC, SCC in situ; cutaneous squamous cell carcinoma (cSCC); and/or basal cell carcinoma (BCC). Forty-one VMAT fields located on the head and limbs from 32 (21 male and 11 female) patients were included in this current 12-month follow-up analysis. All patients received at least 1 course of radiotherapy.

The VMAT standardised treatment protocol for ESFC has been published previously [10]. Briefly, following referral from a diagnosing clinician, the patient was evaluated by the radiation oncologist who defined a treatment area, including any area of invasive disease requiring a higher radiation dose delivered by simultaneous integrated boost. Target treatment volumes were determined by planning computerized tomography scan and subsequently, dosimetry was calculated accommodating bolus thickness. The recommended dose was 45 Gray (Gy) in 25 daily fractions delivered over 5 weeks to the low-risk volume, and at least 55 Gy in 25 fractions to areas of invasive cancer using a Simultaneous Integrated Boost (SIB). Patients were assessed throughout the 5 week treatment period and at 3, 6, 12, and 18 months after treatment, followed by annual reviews.

Efficacy was measured by clinicians’ visual assessment of the field, utilizing clinical photography where available, to determine the percentage reduction of pathology within the treatment field from baseline [11], persistence of existing lesions, and the development of new or recurrent lesions within the 12-month follow-up period. Lesion treatment failure was defined as the lesion having not clinically resolved post-treatment course, and lesion recurrence when the lesion cleared, but recurred, within the 12-month time point. New lesion occurrence was defined as those lesions that appeared within the treated field where none were documented prior to radiotherapy.

All lesion descriptions, field definitions, toxicities, and efficacy assessments were provided by either the treating dermatologist or radiation oncologist. Despite extensive efforts, in this retrospective registry, some data are missing at certain timepoints which have been noted.

The primary end point for this review was >90% clearance of the treatment field, with the appearance of isolated keratoses at 6 or 12 months considered not significant. Treatment failure for field therapy was defined as either not ever achieving >90% clearance of the field, or a loss of improvement (<90% clearance) after prior successful clearance. For lesions such as invasive keratinocyte cancers treated with conformal radiotherapy (±SIB), treatment success was defined as clinical resolution of the lesion post-treatment course.

The Lovett Score of skin cosmesis [12] described the physician-assessed cosmetic outcome. The Lovett Score defines; “excellent cosmesis” as no telangiectasia, pigment change or fibrosis; “good cosmesis” as mild telangiectasia or slight pigment change; “fair cosmesis” as severe telangiectasia, or pigment change or mild-to-moderate fibrosis; and “poor cosmesis” as severe fibrosis or skin contracture.

Toxicities were documented using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.16 [13]. Toxicities that were identified in the field, but not coded in the CTCAE were graded by the relevant system’s organ class using the CTCAE term “other.” The NDROR definitions of these toxicities are described in the footnotes of Table 1 (outcomes of safety and tolerability are discussed in the Results section) NDROR received ethics approval from Bellberry Ltd (Approval Number: 2017-04-288-A-3) and is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR); reference number: ACTRN12618000627257.
Results

The patients in this series ranged from 49 to 88 years of age at the time of treatment (mean 73.6 years). Lesions were diagnosed clinically or histopathologically and included SCC in situ, cSCC; and/or BCC. Table 2 shows the incidence of the “within field” lesion types identified prior to radiotherapy treatment. All patients had between 1 and 3 lesion types within a field.

Lesion types included field cancerization ($n = 17$); cSCC ($n = 15$); BCC ($n = 10$); SCC in situ ($n = 7$); and/or benign/other lesions ($n = 3$). The following anatomical areas: face including cheek ($n = 4$), forehead ($n = 5$), nose ($n = 5$); leg (knee to ankle) ($n = 9$); scalp ($n = 11$); ear ($n = 3$); hand ($n = 2$); and foot ($n = 2$) were treated. Previous treatments included a combination of 5-fluorouracil, curettage; other topical therapies, and/or surgical excision.

For the 41 fields treated with VMAT, fields received a mean (SD) dose of 47.9 Gy (SD 7.4; range 23.4–60) over an average of 23.9 fractions (SD 3.8; range 13–30). In general, VMAT was utilized for the wide-field treatment of regional ESFC including keratinocyte cancers.

Efficacy Outcomes at 12 months

Thirty-six fields (87%) achieved a clinical clearance of over 90% (see Table 3). Of those, 33 (80%) fields achieved complete clearance of visible actinic keratosis or keratinocyte cancers within the treated field, with 3 (7%) fields demonstrating 91–99% clearance of lesions, and no treatment failure. Two newly occurring lesions (1 BCC and 1 SCC in situ) were identified within a treated field at 12 months.

Safety and Cosmetic Outcomes at 12 months

Table 1 summarizes the reported toxicities at 12-month post-treatment. Of note, toxicities reported in more than 5% of cases at 12 months included: alopecia ($n = 4$); dryness ($n = 3$); erythema ($n = 2$); and telangiectasia ulceration ($n = 4$). All reported toxicities at 12 months were grade 1 or 2 only, with no cases of persistent radiation dermatitis.

Table 1. Toxicities reported at 12 months according to CTCAE version 5.0.16 toxicity grades

| Toxicity               | Grade 1, $n$ (%) | Grade 2, $n$ (%) |
|------------------------|------------------|------------------|
| Alopecia               | 0 (0.0)          | 4 (11.1)         |
| Erythema*              | 2 (5.6)          | 0 (0.0)          |
| Telangiectasia         | 2 (5.6)          | 0 (0.0)          |
| Ulceration             | 2 (5.6)          | 0 (0.0)          |
| Dryness                | 1 (2.8)          | 2 (5.6)          |
| Hypopigmentation       | 1 (2.8)          | 0 (0.0)          |
| Hyperpigmentation      | 0 (0.0)          | 1 (2.8)          |
| Oozing/crusting**      | 1 (2.8)          | 0 (0.0)          |
| Other                  | 1 (2.8)          | 0 (0.0)          |
| Pain of skin           | 1 (2.8)          | 0 (0.0)          |
| Skin atrophy           | 1 (2.8)          | 0 (0.0)          |

*Erythema defined in the NDROR as superficial reddening of the skin, usually in patches, as a result of injury or irritation causing dilatation of the blood capillaries.

**Oozing/crusting graded by CTCAE version 5.0.16 skin and subcutaneous tissue disorders – “Other” in the NDROR as a collection of inflammatory cells (serum, pus, or blood and fibrin) in the superficial portion of the epidermis.
The Lovett Score, as measured by the treating dermatologist, showed improved cosmetic scores of the field \((n)\) excellent \(n = 25\ (61\%);\) good \(n = 9\ (22\%);\) and fair \(n = 1\ (2\%).\) There were no fields with a poor cosmetic outcome. Example images of a cosmetic treatment outcome are shown in Figure 1.

**Conclusion**

The high rate of complete clearance at 12 months seen in this case series, compares very favourably with other treatments, including topical 5-fluorouracil, imiquimod, and photodynamic therapy [1, 3, 4]. Our case series also suggests that radiotherapy is potentially a durable
salvage option following previous treatment failure. One explanation for its efficacy is that VMAT technique can deliver targeted doses to target volumes up to a depth of 5mm, thus including skin appendages, such as sweat glands and hair follicles, potentially alleviating sanctuary sites for malignant keratinocytes [14].

Toxicities reported in our patient population demonstrated that VMAT was well tolerated at 12-month post-treatment. The maximum CTCAE grade recorded was 2, involving 1 patient with residual dryness of the skin, 1 patient with pigmentation changes, and 3 patients with alopecia. Alopecia was of minimal impact as it did not involve a cosmetically sensitive area, such as the scalp or eyebrow. It is also of note, that large fields on the lower legs treated with VMAT were included in this registry, areas for which traditional radiotherapy would not have been used.

This case series analysis has several limitations, including its retrospective nature, small cohort size, and short length of follow-up. Further, as a result of the registry design, some data are missing. Reports of topical therapies have described larger sample sizes [15, 16]. Notwithstanding, smaller studies have enabled valuable findings, for example, a cohort of 16 patients was sufficient to indicate that radiotherapy could potentially be used to clear extensive actinic keratosis [7]. A larger series with a longer follow-up interval may reveal unexpected late toxicities not seen thus far in our cases. A further limitation is the heterogeneity of the lesion type.

Fig. 1. ESFC example of prior and post VMAT at 12 months. a Prior to radiotherapy: extensive solar damage, including SCC in situ treated with 50 Gy in 25 fractions using VMAT. b 12-month post-treatment; 1 very small healing ulcer. On completion of treatment, this patient subsequently presented with hair growth on the scalp which was previously not present. The hair growth was prolifically present and had regrown, black in colour (his original hair colour as a youth). c Prior to radiotherapy: multiple non-melanomatous skin cancers treated with 45 Gy in 25 fractions using VMAT. d 12-months post-treatment.
Registries provide effective means for assessing long term radiotherapy outcomes [16]. This positive collaboration between Australian dermatologists and radiation oncologists demonstrates favourable efficacy, safety, and cosmetic outcomes at 12 months. VMAT treatment may play a growing role in future therapy for ESFC.

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Statement of Ethics

The NDROR was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000627257), received ethics approval from Bellberry Ltd (Approval Number: 2017-04-288-A-3), was conducted in accordance with ethical principles founded in the Declaration of Helsinki and the Declaration of Tapei, and all participants provided written informed consent.

Conflict of Interest Statement

L. Spelman, C. Baker, and R. Sinclair are paid advisers for the NDROR and GenesisCare. L. Spelman, D. Christie, and C. Baker are unpaid members of the advisory panel that consults on the guidelines for the NDROR. A. Kaminski and D. Christie are paid employees of GenesisCare.

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Author Contributions

Conceived the concept of this work and designed the study: L.S., R.S. Involved in the conduct of the study and contributed to data collection: R.S., L.S., M.S., A.K., D.C. Contributed to data analysis and interpretation of the results: L.S., R.S., M.S., D.C., C.B., A.K. Manuscript writing and revision for intellectual content: L.S., R.S., M.S., D.C., C.B., A.K. Approved the final version of the article: L.S., R.S., M.S., D.C., C.B., A.K. Guarantor of the article: L.S.

Data Availability Statement

Research data are stored in an institutional repository and will be shared upon reasonable request and with permission of GenesisCare Pty Ltd. by emailing.
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