UK SPOT Protocol: VMAT treatment for Extended Skin Field Cancerisation (UK)

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1. Introduction and Purpose

GenesisCare is committed to delivering its strategic and operational objectives in accordance with all applicable legislation, standards, and principles of good governance.

To describe GenesisCare UK protocol for the treatment, planning, QA, and outcomes for extended field VMAT external beam radiotherapy treatment of invasive and in-situ keratinocytes (excluding Merkel Cell Carcinoma). The implementation and use of this protocol, aims to standardise the treatment of patients with extended field cancerisation.

2. Terms and Definitions

Abbreviation	Explanation
BCC	Basal Cell Carcinoma
SCC	Squamous Cell Carcinoma
cSCC	Cutaneous Squamous Cell Carcinoma
In Situ SCC	Bowens disease, EIC (Intraepithelial Carcinoma) – all are synonyms for pre-invasive cSCC
EFSC	Extended Field Skin Cancerisation
VMAT	Volumetric Modulated Arc Therapy
IMRT	Intensity Modulated radiotherapy
MDM	Multi-disciplinary Meeting
MDT	Multi-disciplinary Team
MPE	Medical Physics Expert
OAR	Organ at Risk
GTV	Gross Tumour Volume
ITV	Internal Target Volume
PTV	Planning Target Volume
RT	Radiation Therapist
OMS	Oncology Management System
RO	Radiation Oncologist
MPE	Medical Physics Expert
SIB	Simultaneous Integrated Boost
CT	Computed Tomography
CBCT	Cone Beam CT
TNM	Tumour, Node, Metastases: staging system
Extended field	Treatment fields > 50cm^2 (1)

3. Scope

This document applies to the prescription and treatment protocol for all patients scheduled to receive extended field VMAT external beam radiotherapy treatment of invasive and in-situ keratinocytes.

4. Responsibilities

Radiation oncologists require credentialing to prescribe extended field VMAT treatments. Peer review of cases will be used to provide supervised training as well as oversight of treatment according to the protocol, and to ensure that potential supportive care needs have been identified and appropriately addressed. More detail regarding peer review and credentialing requirements are set out in Appendix 1 (refer to GenesisCare training and competency framework documents).

5. GenesisCare Clinical Procedure for VMAT treatment for extended field skin cancerisation

5.1. Patient Selection

5.1.1 Inclusion Criteria

Diagnosis

- Fields of in situ SCC; Bowens disease; EIC (intraepithelial carcinoma) – preinvasive cSCC; Solar/actinic keratosis
- Fields can also harbour active invasive lesions:
  - Basal cell carcinoma (BCC)
  - Cutaneous Squamous cell carcinoma (cSCC)
- Treatment without a biopsy may be indicated in specific cases, particularly where the referring specialist is clinically confident of a diagnosis.

Staging

- For field cancerisation: use Tis in OMS;
- For lesions in field, the TNM staging can be used

Aim

- Durable local control of field cancerisation with preservation of skin integrity and appearance, relief of symptoms, improvement in Quality of Life.

- Curative for individual localised invasive lesions
- NOTE that in some patients (e.g. elderly, frail, or significant comorbidities) the aim of treatment may *not* be to entirely clear the treatment field. In this setting consideration should be given to a low dose protocol.

5.1.2 Exclusion Criteria

Absolute exclusions

- Invasive melanoma
- Merkel Cell Carcinoma
- Known radiation sensitivity syndrome (e.g. Ataxia-telangiectasia, Gorlins syndrome)
- Treating both lower limbs concurrently

Relative exclusions

- Established diagnosis of connective tissue disorder such as scleroderma or systemic lupus erythematosus, predisposing to increased radiation toxicity

Cautions

- Immuno-suppressed patients
- Young age (<50yrs) due to potential risk of radiation carcinogenesis
- Potential inability to comply with course of treatment
- Concurrent systemic treatment including chemotherapy and new targeted drugs
- Concurrent use of radio-sensitising drugs for medical comorbidities (e.g. methotrexate, hydroxy urea, etc.)
- Lower limb treatments in patients with peripheral vascular disease including chronic venous stasis, lipodermatosclerosis, diabetes
- Potential predisposition for lymphoedema and previous lymphadenectomy
- Prior high dose radiotherapy to the same treatment site
- Treating bilateral widefield face concurrently

NOTE: Any patient who meets one or more of the exclusions and/or cautions must go to peer review via the UK Skin MDT, held each Wednesday. Radiation oncologists and radiation therapists are responsible for identifying patients for peer review.

5.2. Required dataset for referral

For a referral to be deemed adequately referred, the following information is required from the consultant and associated physicians:

- Clinic Letter
- MDT report
- Booking form
- Agreement to treat
- Referral Letter from referring specialist to oncologist (if applicable)
- Histopathology (if applicable)
- Imaging (if applicable)

5.3. Timing and Sequencing

Many patients being considered for extended skin field treatment are likely to have had long standing non-invasive skin changes, hence the timeframe for commencing radiotherapy is unlikely to be critical to a favourable outcome. Consideration should be given to patients' individual circumstances to maximise likelihood of completing the prescribed course of treatment.

If 3D printed bolus is to be employed for the treatment site, two simulation sessions (e.g. scalp, nose, limbs) approximately one week apart may be required. The time from second simulation to commencement of treatment will be scheduled according to local timelines.

Refer to Section 5.8 regarding the mandated break in treatment

5.4. Imaging Requirements

No specific pre-treatment imaging required unless clinically indicated.

5.5. Simulation

5.5.1 Patient positioning and stabilisation requirements

Patient set up in a stable and reproducible position suitable for VMAT treatments.

Refer to relevant SPOT CT work instruction (RT-WI-428) for further guidance on patient positioning and stabilisation.

5.5.2 Field delineation

RO to attend simulation session to delineate fields on skin and discuss potential issues associated with set-up, dosimetry, and treatment related requirements.

It is the RO's responsibility to ensure that there is understanding between field delineation and CT imaging and this is communicated to RT.

Refer to SPOT CT work instruction (RT-WI-428) and planning documentation: SPOT UK SOP (PHY-SOP-103) and SPOT Eclipse planning (PHY-WI-156).
NOTE: RO CT marks = CTV (circumferentially & cranio-caudally)

5.5.3 Bolus

Determine if 3D printed bolus can be used for the treatment site.

If 3D bolus is not utilised, the following bolus is recommended:

- Scalp and limb:
  - Minimum 8mm bolus
  - Bolus is to be constructed to the patient with minimal air gaps. Where air gaps are detected, consult with MPE, local/ national SPOT team.

Refer to SPOT CT work instruction (RT-WI-428) and 3D bolus creation (PHY-WI-110).

5.5.4 CT Markers and wires

Mark the following with CT compatible wire

- Fully mark CTV field borders
- Mark all lesions that require SIB (mark CTV for lesions requiring SIB)
- Mark any previously treated areas with wires
- Mark areas that need to be avoided e.g. active benign ulcers, hair bearing skin such as eyebrow

5.5.5 CT simulation

Refer to SPOT CT work instruction (RT-WI-428) and CT Set up sheet (SPOT section) (RT- TEM-387).

5.5.6 Site photographs and field tracings

Ensure plastic/vinyl tracings and photos are captured which accurately show the lesion, lesion edges and surrounding anatomy to enable future identification of the lesion and extent of the treated area. Use medical ruler with patient and lesion identification to indicate the scaling of the lesion.

If a thermoplastic mask is used, ensure photographs are taken to clearly demonstrate borders of marked fields, with and without wire (with immobilisation mask removed).

Refer to SPOT Clinical photography of Skin (RT-WI-429).

5.6. Target Delineation & Margins

Structure	Description
Gross Target Volume (GTV)	Macroscopic disease as required
Clinical Target Volume (CTV)	3mm - 5mm rind inside patient's skin between marker wires depending on palpable thickness and clinical context
PTV radial expansion	2mm expansion of CTV deeper into patient and beyond wire field edge 5mm expansion into Bolus (to account for potential oedema during treatment)
PTV superior and inferior expansion	CTV + 5mm
PTV Eval*	PTV cropped inside the patient external contour where the patient contour includes bolus of at least 8mm thickness. Used for reporting along with PTV

* PTV Eval is a planning structure that is created for dose optimisation to ensure skin surface dose is maintained in the presence of small contour or set-up variations.

5.7. Dose Prescription and Fractionation patterns

5.7.1 Total Dose

NOTE: Peer review is required for prescription outside of this protocol. Further, extended skin fields of areas not described must undergo peer review.

Fractionation Scheme for Extended Skin Field Treatment to torso and head	Dose & Fractionation
Fully Fractionated: 5 weeks	Extended skin field of the torso and head: 45-50Gy in 25 fractions of 1.8-2.0Gy per fraction Simultaneous Integrated Boost:

	Total dose of 55-60Gy in 25 fractions of 2.2-2.4Gy per fraction Whole nose: 60Gy in 30 fractions of 2.0Gy per fraction (must be peer reviewed) 45Gy in 25 fractions of 1.8Gy per fraction to whole nose with 55Gy/25 fractions of 2.2Gy per fraction boost
Sub-total nose or scalp - intermediate fractionation size: 4 -5 weeks NOTE: Not to be used for whole scalp treatment	Scalp/Nose: 50-55Gy in 20-25 fractions of 2.2-2.5Gy per fraction

Curative Fractionation Scheme for Extended Field Limbs	**Dose & Fractionation**
Fully Fractionated: 5 weeks	Limbs: 45Gy in 25 fractions of 1.8Gy per fraction SIB Boost: Total dose of 55-60Gy in 25 fractions of 2.2-2.4Gy per fraction Mandatory break of at least 2 weeks - duration after 10 fractions* RO to review patient prior to recommencing treatment following break. RO to assess: • Limb oedema • Pain • Desquamation in the treated limb

Dose and fractionation reference: Potter et al. (2019)

*See Appendix 1 for the Rationale for a break in the treatment of limb

5.8. Organs at Risk

All organs at risk (OAR) must be contoured and will be used for dose reporting. Where possible try to spare hair. If treating hair bearing skin, use CT wires and aim for <30Gy.

Treatment Site	Organ (entire structure)	Dose Goal - Primary	Dose Goal – Variation Acceptable
Scalp/head*	Brain	Mean D < 8Gy	Mean D 8-12Gy minor deviation
	Lens	Max < 6Gy	<10
	Lacrimal Gland [1]	Max < 30Gy Mean D < 25Gy	
	Normal Tissue	ALARA	
	Inner ear	Mean <40Gy	
Face	Parotid	Mean <25Gy	
	Lens	Max < 6Gy	<10
	Lacrimal Gland [1]	Max < 30Gy Mean D < 25Gy	
	Nasolacrimal duct (optional)	Mean <30Gy	
	Nasal Septum	Mean <25Gy	<30
	Normal Tissue	ALARA	
	Oral cavity	Mean <20Gy	
	Lips (optional depending on technique)	Mean <30Gy	
	Inner ear	Mean <40Gy	
	Anterior third of the globe	Mean <30Gy	
Torso	Spinal cord	Max <45Gy	
	Lung	Mean <5Gy	
	Liver	Mean <30Gy	
	Thyroid	Mean <30Gy	Mean <40Gy

Treatment Site	Organ (entire structure)	Dose Goal - Primary	Dose Goal – Variation Acceptable
Limbs	Lymphatic Protection/Avoidance of Lymphoedema	No mean dose data available. Recommend 18-20Gy isodose line should not be overlapping the skin sparing strip. * 1. Limb sarcoma literature suggests leaving a 20% to 25% circumferential preservation strip along a section of the limb where Lymphatics are thought to traverse.[2] 2. Use of a split course technique (mandatory break of at least 2 weeks duration to allow for resolution of acute symptoms) to reduce risk of lymphoedema	
	Other normal tissue – Contralateral leg, Torso	ALARA	

*NOTE: Any plans that do not include a skin sparing strip must be discussed at Peer Review

6. Treatment Planning & Dosimetry

6.1 Planning, Normalisation & Plan Evaluation
Refer to relevant RT planning documentation, PHY-WI-156.

7. Quality Assurance

In vivo dosimetry, if required, should be reported by fraction 3 or prior to delivery of 10% of the prescription dose to confirm accurate dose delivery.

Patient specific pre-treatment QA is required on all VMAT cases and must be completed showing a pass result before the delivery of the first fraction.

Documentation detailing the Quality Assurance results should be available in OMS.

Refer to relevant QA document, PHY-WI-262.

8. Treatment

8.1. Image Verification

Treatment verification should be performed daily. If there is oedema resulting in a change in diameter of more than 1.0cm, RO, MPE and local planning team to be notified for clinical review of dosimetry and consideration of re-planning or treatment break.

Refer to Varian image guided radiotherapy (IGRT) SOP (RT-SOP-412) -SPOT section.

9. Treatment Review: Toxicity & Outcomes Reporting

On-Treatment and Post-Treatment review by RO weekly, with or more frequently if required.

On-Treatment & Post-Treatment Toxicity and General Health Reviews (including dressings, education, and supportive care) to be conducted and managed by an entitled therapy radiographer or nurses weekly or more frequently if required.

Refer to SPOT Clinical photography of Skin (RT-WI-429), SPOT skin assessment work instruction (RT-WI-446) and SPOT MOSAIQ patient data entry work instruction (RT-WI-442).

10. Patient Follow-up & Data collection

10.1. Patient follow-up

Clinical consultation at 4-6 weeks post treatment or as clinically indicated.
6 and 12 months after completion of radiotherapy.

10.2. Minimum Data Set

Prospective data collection should include the following:

1. OMS number
2. Patient name
3. Patient date of birth
4. Patient gender (F/M)
5. Treating physician
6. Date of diagnosis
7. Eastern Cooperative Oncology Group (ECOG) status
8. Histology
9. Dose / prescription

10. Dmax, Dmin and mean PTV dose
11. Acute side effects as applicable:
    a. Radiation dermatitis
    b. Pain
    c. Oedema
12. Treatment outcome
    a. Lovett cosmesis score
    b. Clinical clearance
    c. Skin toxicity

On treatment review MDS:

Symptoms:

1. Pain (drop down including low and no analgesia; medium and requiring analgesia; etc)
2. Patient reported swelling

Signs:

1. Tenderness
2. Erythema
3. Skin integrity
4. Tumour lysis syndrome

11. References and related documents

- [1] Fogarty, Christie, Spelman et al; https://biomedres.us/pdfs/BJSTR.MS.ID.000998.pdf
- Potter, A., Price, M., Papworth, D., Melven, L., Shaw, I., Hayles, M., Hellyer, J., Buman, K., Kaminski, A., Schlect, D., Wong, B., Christie, D., A Izard, M., E Holt, N. and B Fogarty, G., 2020. A technique for treating extended skin field cancerisation using volumetric modulated arc therapy. *International Journal of Radiology & Radiation Therapy*, 6(4), pp.111–119.
- B Fogarty, G., RH Christie, D., Kaminski, A. and E Potter, A., 2018. A radiation oncology approach for using definitive radiotherapy with volumetric modulated arc therapy (VMAT) for skin field cancerisation (SFC). *International Journal of Radiology & Radiation Therapy*, 5(4).
- B Fogarty, G., Christie, D. and Potter, A., 2019. Volumetric modulated arc therapy (VMAT) for extended skin field cancerisation (ESFC): Radiobiological learnings from unique patient cases. *International Journal of Radiology & Radiation Therapy*, 6(5), pp.156-162.
- SPOT CT Work Instruction: RT-WI-428

- SPOT Varian Edge & Align RT Work Instruction: RT-WI-430
- SPOT Clinical photography of Skin: RT-WI-429
- SPOT Skin Assessment Work Instruction: RT-WI-446
- SPOT MOSAIQ Patient Data Entry Work Instruction: RT-WI-442
- SPOT Referral Checklist: RT-TEM-449
- CT Set up sheet (SPOT section): RT- TEM-387
- Varian IGRT SOP: RT-SOP-412
- PHY-WI-110: 3D-Bolus creation
- PHY-WI-156: SPOT Eclipse planning
- PHY-SOP-103: SPOT-UK SOP
- PHY-WI-262: PSQA for SPOT patient – Point Doses, Mobius & ArcCheck

12. Appendices

- Appendix 1 - Rationale for treatment break for limbs

Revision History

Version	Date Created	Created By	Description of change
1.0	02/09/2020	Clinical Oncologist: Richard Shaffer Principal Physicist: Hussein El-Shaer Skin and Benign specialist Radiographer: Rory Walford	Creation of Document
1.1	November 2020	Sanell Pienaar, Compliance Manager	Document Authoriser updated to reflect recent changes in the company

Appendix 1 - Rationale for treatment break for limbs

The break in treatment (see 5.8) for patients having treatment for field cancerisation of limbs has been mandated due to the acute inflammatory process occurring in the skin after doses as low as 18Gy. Pilot experience in Queensland with extended field skin cancerisation treatment indicates only a small percentage of patients will complete a fully fractionated schedule without a break in treatment due to toxicity. The toxicities encountered included pain (often requiring opiates), acute oedema and large areas of desquamation corresponding to the actinic skin changes. These toxicities often led to the need for a more prolonged treatment break later in the patient's treatment course. Although radiobiological data from other treatment sites cautions the use of a treatment break due to the potential for accelerated repopulation in lesion-based treatment, (Bese et al., 2007) the dose/response/time relationships may be different for UV induced extended field skin cancerisation. Prospective data collection on NDROR and the forthcoming Phase 2 protocol will help provide more evidence.

Additional considerations for this patient group include their advanced age which is associated with a reduction in underlying stem cell number (Maimets et al., 2015), and comorbidities including chronic vascular changes. It may be possible to avoid a break in younger patients without comorbidity requiring treatment to upper limbs, but a treatment break should be given to all lower limb patients.