

## Incidental Long Term Control of Recalcitrant Rosacea Following Modern Radiotherapy – A Case Series

Gerald B. Fogarty<sup>1</sup>, Nicola Holt<sup>1</sup>, Tiarna Shearer<sup>1</sup>, Mark Wanklyn<sup>1</sup>, Aoife Conway<sup>1</sup>, Jacqueline Kramer-Maier<sup>2</sup>, Tanya Gilmour<sup>3</sup>, Stephen Shumack<sup>4</sup>

1 Genesiscare Radiation Oncology, Mater Hospital, 25 Rocklands Rd, Crows Nest, NSW, 2065, Australia;

2 Sun Doctors, Frenchs Forest, 28 Forest Way, Frenchs Forest, NSW, 2086, Australia;

3 North Shore Dermatology & Specialist Skin Cancer Centre, 39 East Esplanade, Manly, NSW, 2095, Australia;

4 Department of Dermatology, Royal North Shore, St Leonards, NSW, 2065, Australia.

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**Correspondence to:** Gerald Fogarty, Genesiscare Radiation Oncology, Mater Hospital, 25 Rocklands Rd, Crows Nest, NSW, 2065, Australia.

**Email:** [Gerald.fogarty@genesiscare.com](mailto:Gerald.fogarty@genesiscare.com)

**Telephone:** +612 9458 8050

**Fax:** +612 9929 2687

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### ABSTRACT

Rosacea is a common chronic illness with no known durable cure. We present 4 cases of incidental long-term control of recalcitrant rosacea following definitive volumetric modulated arc therapy (VMAT) radiotherapy for basal cell carcinoma (BCC) arising within extensive skin field cancerisation (ESFC). At last follow up at an average of 21 months post radiotherapy (RT), all cases had complete response (CR) of the BCC and ESFC. These four cases also had enduring response

of recalcitrant rosacea within and also immediately outside the planning target volume that was prescribed radiotherapy to 45 Gray (Gy) (PTV45). The durability of rosacea control was associated with target volumes at least receiving an average of 36.5 Gy in an average of 22.5 fractions. Progression to a prospective trial and the design is discussed.

**Key words:** Rosacea; Radiotherapy; Face; Nose; Skin; Australia; Rhinophyma; Volumetric Modulated Arc Therapy; Quality of Life; Case Reports; Retrospective Studies

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### INTRODUCTION

Rosacea is a common chronic relapsing inflammatory skin condition which mostly affects the central face<sup>[1]</sup>. The cause is unknown<sup>[2]</sup>. It is initially characterised by transient flushing followed by persistent erythema and skin inflammation and may progress to phymatous rosacea characterized by thickened, cosmetically disfiguring skin<sup>[3]</sup>. The pathophysiology is thought to be a dysregulation of the immune system, brought about by microbes of the normal skin flora<sup>[4]</sup>. It can seriously affect quality of life<sup>[5]</sup>.

There are many treatment modalities offered but a definitive durable cure has yet to be found<sup>[6]</sup>. Symptomatic exacerbations are treated with topical creams, and oral therapies aimed at decreasing pathogen load<sup>[7,8]</sup>. A Cochrane review<sup>[9]</sup> of 106 studies showed no durable cure. The longest follow up in this study was 40 weeks post treatment so any treatment with durable control still at 12 months post therapy can be considered long term in this disease. Radiotherapy was not included in this study.

Radiation therapy (RT) has undergone a revolution in the last few years due to the advent of modern technologies like volumetric modulated arc therapy (VMAT)<sup>[10]</sup>. Convex skin surfaces like scalps and

noses that harbour extensive skin field cancerisation (ESFC) can be treated with durable control even around the head and neck<sup>[11]</sup>. ESFC can contain and promote multifocal invasive malignant skin cancers like basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC). When these arise within ESFC they are especially amenable to this treatment<sup>[12]</sup>. RT cures malignancy without the tissue loss of surgery, resulting in better functional and cosmetic outcomes, especially in areas where tissue loss would be obvious, like the nose. This may result in better quality of life, but more prospective study is needed. The nose is also often involved in the rosacea process, and large fields of rosacea can be incidentally included in and around the definitive VMAT treatment volumes of ESFC involving the nose.

We present four cases of incidental long-term control of recalcitrant rosacea following modern VMAT radiotherapy for invasive skin cancers arising within ESFC involving the central face including the nose.

## CASE SERIES

### Case 1

A fit immune-competent 73-year-old Caucasian woman was referred for radiotherapy (RT) of the entire nose for three biopsy-proven multiple basal cell carcinoma (BCC). BCCs were on the right nasal ala and from the tip of nose going towards left nasal ala respectively (See Figure 1 A). She had over a 20-year history of rosacea. She had used topical therapies such as metronidazole and ivermectin creams, and oral systemic doxycycline, with no durable improvement. She was resigned to treating the rosacea when symptomatic, which was then several times per year, leading to significant cost and discomfort.

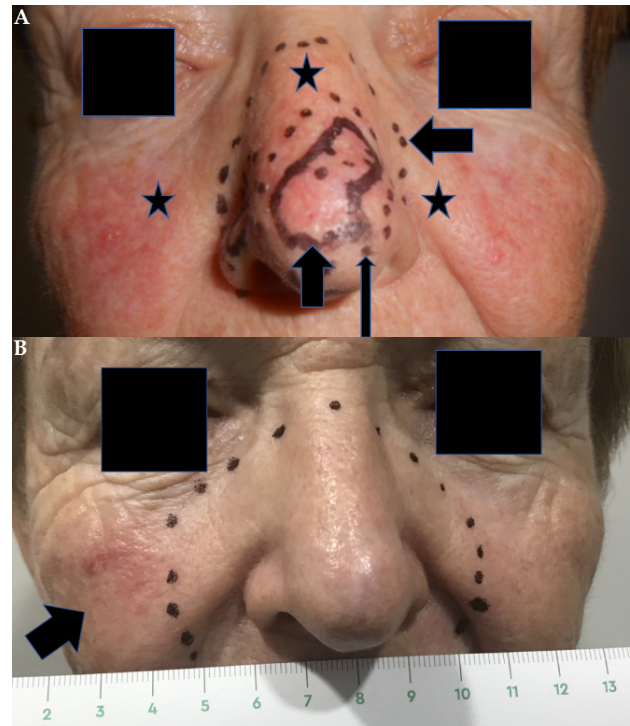
She was treated with volumetric modulated arc therapy (VMAT) according to our protocol<sup>[13]</sup> for ESFC. The RT plan involved three volumes of simultaneous integrated boost (SIB) within a whole nasal skin volume. To treat the invasive disease, the SIB volumes were treated to a total dose 55 Gray (Gy). The whole nose volume was treated to a total dose of 45 Gy, which is sufficient for insitu ESFC. The treatment was given in 25 fractions with no planned break. In vivo dosimetry (IVD) confirmed the planned dose was delivered. Her skin toxicities were the expected side effects of in-field erythema, desquamation and mucositis<sup>[12]</sup>. These were looked after on a conservative basis by our nursing staff. She had a complete response at 4 weeks post RT as far as the BCC were concerned. See Figure 1 A and B.

Nine months following the completion of RT on routine review she requested further RT to a patch of symptomatic rosacea on the lateral right cheek outside previous high dose field. At that stage she had incidental long-term control of recalcitrant rosacea in the field of ESFC treated with VMAT. She had required no more rosacea treatment since the RT. She also had clearance of her rosacea immediately outside her previous planning target volume<sup>[14]</sup> that had been treated to 45 Gray (Gy) (PTV45) (Figure 1 B). Clearance continues at 18 months.

To calculate the RT dose responsible for clearing the rosacea, a template was taken<sup>15</sup> outlining the area that was symptomatically and clinically free of rosacea. This was used to create a new volume that was contoured onto the original planning computer tomography scan (CT). The dose parameters of that volume were then calculated. Rosacea clearance corresponded to a volume that was within the 35Gy isodose line, that is, treated to at least 35 Gy in 25 fractions.

### Case 2

A sprightly 94-year-old independent woman on no medications had VMAT for a two-centimetre biopsy proven infiltrative BCC of the



**Figure 1** Case 1 pre and post RT showing rosacea clearance. (A): Anterior photo taken at RT planning prior to any RT treatment showing extent of gross tumour volume (GTV)<sup>[14]</sup> of large BCC on nasal tip outlined in solid black line (indicated by short thick vertical black arrow). The dotted line of the Planning Target Volume 55Gy (PTV55) of the SIB to treat the BCC surrounds this (indicated by long thin vertical black arrow). This PTV55 is within the Planning Target Volume 45Gy (PTV45) (identified by short thick horizontal black arrow). The black stars indicate areas of symptomatic recalcitrant rosacea, which are both inside and outside the PTV45 treatment volume. (B): Anterior photo taken nine months following RT for BCC nose showing complete response of BCC but also complete and enduring response of rosacea within and immediately outside the PTV45. The dotted line on skin shows area of rosacea control. When compared to Figure 1A, this area includes areas both inside and outside the PTV45 treatment volume. It corresponds to the 35Gy isodose line from the RT plan. The short black arrow indicates an area of persisting symptomatic rosacea for which the patient requested radiation treatment nine months after the initial treatment. This area was well outside the VMAT treated field.

bridge of lower nose within an area of ESFC. She also had a 10-year history of rosacea and had taken topical treatments for symptom relief during exacerbations, usually a few per year. VMAT prescription was 45Gy in 15 fractions given 5 days per week to the nasal bridge area. IVD confirmed the planned dose was delivered. At 9 months post RT she had clearance of the BCC but also had clearance of her rosacea, including areas outside the previous PTV45 field (Figure 2 B). Clearance continues at 16 months. This has required no more rosacea treatment since the RT.

To estimate the dose of radiotherapy needed for rosacea clearance, the same procedure was completed as in case 1 but using photos. Clearance corresponded to the volume of skin within the 35 Gy isodose line, that is, the volume of skin that had received at least 35 Gy in 25 fractions. A persisting rosacea lesion on the right lateral cheek received a mean dose of 4.8Gy and was not controlled at this dose.

See Figure 2 A and B.

**Case 3**

A 74-year-old male had had multiple operations including Mohs surgery for BCC of the nose and had a further BCC recurrence and he was referred for tissue conserving RT. He had also been suffering from the rhinophyma variant of rosacea for 15 years and had had both topical and oral treatments multiple times for symptomatic exacerbations. He was treated with VMAT to a total dose of 52.8 Gy to a solitary SIB. This was within a VMAT field treated to 43.2Gy in 24 fractions. His treatment was stopped a fraction short of the full prescription of 45Gy in 25 fractions due to acute toxicity, a common practice in our VMAT for ESFC experience<sup>[6]</sup>.

20 months post VMAT he had complete response of BCC but also a partial and enduring response of rhinophyma rosacea. He has required no more rosacea treatment since the RT. Following the method of dose calculation above in case 1, the volume of skin with clearance of rosacea corresponds to the 38Gy isodose line, that is, skin that had received at least 38Gy in 24 fractions. Clearance continues at 27 months. See Figure 3A and B.

**Case 4**

A fit 72-year-old male had a history of BCC on the nose treated



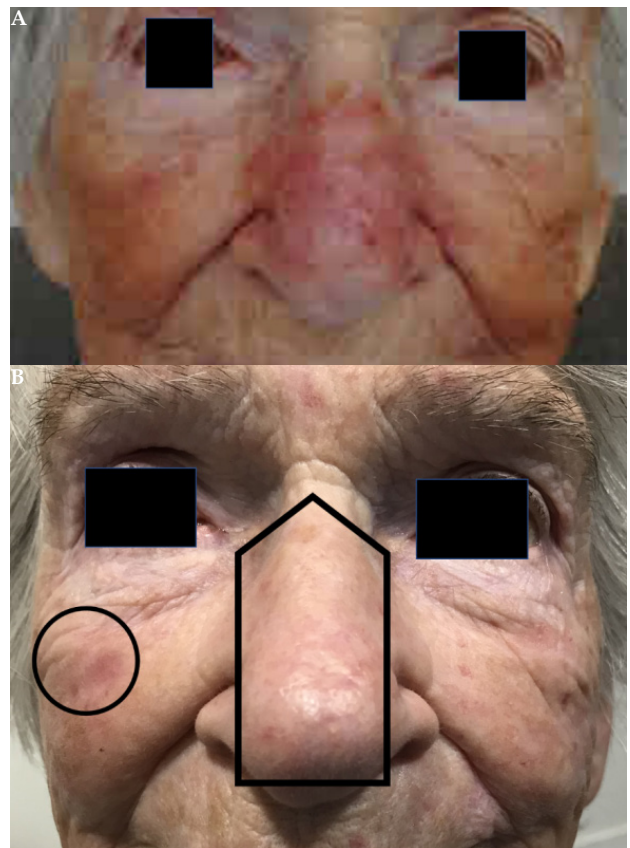
**Figure 3** Case 3 pre and post RT showing rosacea clearance. (A): Photo showing rhinophyma prior to RT. (B): Photo 20 months post VMAT showing complete response of BCC but also partial and enduring response of rhinophyma rosacea. Unfortunately, the asymmetry caused by tissue sacrifice by the previous Mohs surgery to right nasal alar is also more apparent.

with Mohs surgery but had recurred and was referred for VMAT field therapy to 45 Gy with SIB to 55 Gy, all in 25 fractions. The SIB was for an active biopsy-proven BCC on the right nasal alar. In vivo dosimetry confirmed the planned dose was delivered. He also had an eight-year history of rosacea and had taken topical treatments for symptom relief during exacerbations. At 18 months he had a complete clearance of the BCC but also enduring clearance of his rosacea both inside and outside the VMAT PTV45 treatment volume. The rosacea clearance corresponds to the 38Gy isodose line. Clearance continues at 25 months. See Figure 4 A and B.

**DISCUSSION**

We present 4 cases of incidental long-term control of recalcitrant rosacea following definitive VMAT radiotherapy for BCC within ESFC. At last follow up all cases had complete response of the BCCs but also had enduring response of rosacea within and immediately outside the PTV45 area. Patient and treatment details are summarised in table 1. The investigation of this phenomena started when the patient in case one asked for treatment of rosacea arising outside the treated VMAT skin field, and when dermatology colleagues remarked how VMAT had also provided durable local control for patients treated for ESFC and who had also suffered recalcitrant nasal rosacea over many years.

Rosacea is a common chronic relapsing inflammatory skin condition which mostly affects the central face. It affects between



**Figure 2** Case 2 pre and post RT showing rosacea clearance. (A): Planning photo prior to RT showing rosacea of nose and face. B: Photo nine months following RT showing complete response of BCC but also complete and enduring response of rosacea both inside and outside the VMAT treated field which is shown in the pentagon shape. The black circle shows persisting rosacea on lateral right cheek. This area was well outside the VMAT treated field.



1 and 10% of the population, with those most affected being older female Caucasians<sup>[3]</sup>. The cause is unknown. Diagnosis is based on symptoms, the most distressing being itching, burning and stinging. Risk factors include a family history and factors that worsen the condition include heat, exercise, sunlight, cold, spicy food, alcohol, menopause, psychological stress, and steroid cream on the face<sup>[16,17]</sup>.

Rosacea has four broad subtypes which follow more or less a chronological deterioration with age. Initially there is erythematotelangiectatic rosacea with transient flushing followed by more persistence, and escalating to persistent erythema due to repeated vasodilation, then telangiectasia and skin inflammation in the form of papules, pustules, lymphoedema and fibrosis called papulopustular rosacea, which presents in a Maltese cross distribution over the nose, forehead, cheeks and chin. Circumoral and periorbital areas are typically spared. Phymatous rosacea is characterized by thickened, cosmetically disfiguring skin due to the hypertrophy of sebaceous glands and connective tissue with associated lymphedema and prominent follicular pores. When this involves the nose it is called rhinophyma<sup>[18]</sup> and males are predominantly affected. Ocular rosacea is a late change, commonly causing dry eyes and chronic blepharconjunctivitis, but eventually occurs in greater than 50% of rosacea sufferers<sup>[19]</sup>.

Histodermapathology reveals enlarged, dilated capillaries and venules located in the upper dermis, with angulated telangiectasias, perivascular and perifollicular lymphocytic infiltration, and superficial dermal oedema. The pathophysiology is thought to be a dysregulation of the immune system, as well as changes in the nervous and the vascular system brought about by microbes of the normal skin flora, specifically in the pilo-sebaceous unit in the dermis, that include the Demodex mites and bacteria such as *Staphylococcus epidermidis*<sup>[4]</sup>.

Rosacea has no known cure. Symptomatic exacerbations are treated with topical creams such as brimonidine cream, ivermectin cream, and isotretinoin. Oral therapies aimed at decreasing pathogen load are used such as metronidazole, doxycycline, minocycline, or tetracycline. Local ablative therapies include dermabrasion and laser surgery. Behavioural changes are encouraged to decrease triggers eg regular use of sunscreen and dietary adjustments<sup>[7,8]</sup>. Rosacea can seriously affect a patient's quality of life<sup>5</sup>. A Cochrane review<sup>[9]</sup> of 106 studies revealed that the longest follow up was 40 weeks post treatment. Radiotherapy was not included in that review.

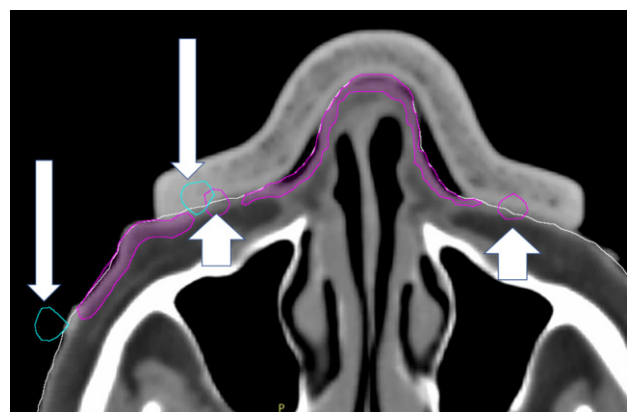
#### Radiotherapy total dose needed for durable response in rosacea

The literature on radiotherapy for rosacea is limited to case studies. Studies written in English are here summarised. Plenk *et al*<sup>[20]</sup> treated 2 patients with nasal skin BCC arising within rhinophyma with orthovoltage to a total dose of 40 Gy in 16 fractions and 39 Gy in 11 fractions respectively. Both had significant partial responses of the rhinophyma. They were followed for 9 and 7 years respectively with no recurrence of either BCC or enlargement of the rhinophyma. Skala *et al*<sup>[21]</sup> treated a 72-year-old with a 10-year history of rhinophyma with 90-kV photons to a total dose of 40 Gy in 20 daily fractions with good partial response and no progression at 7 years. Fairris *et al*<sup>[22]</sup> treated 9 paired sites in 3 patients with a similar condition but of the hands to a total dose of 6 Gy in 6 fractions at one a week and all but 1 had relapsed at six weeks. It seems that a higher dose is needed for rosacea especially if longstanding and recalcitrant to previous topical therapies.

All the cases in this study had durable control of rosacea within the PTV45Gy area. This means that 45 Gy in 25 fractions is an adequate dose. However there was control immediately lateral to the PTV45 in

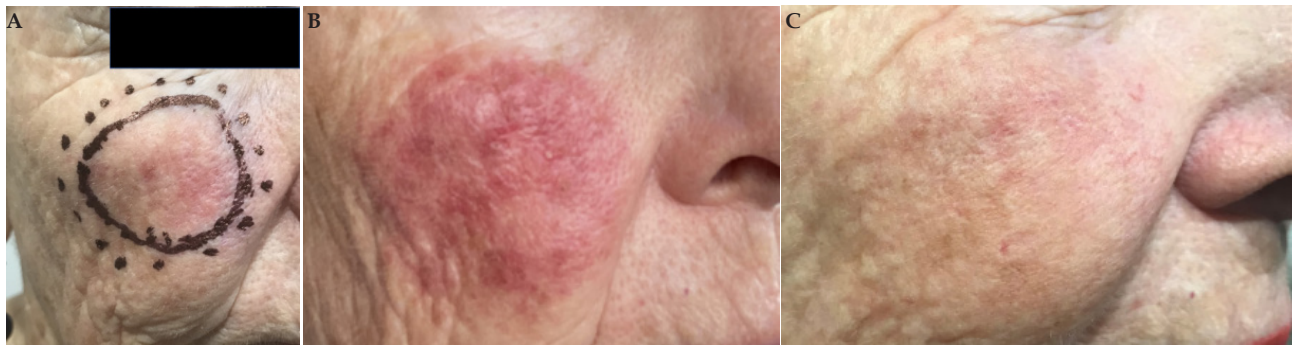


**Figure 4** (A) Planning photo showing PTV55 Gy SIB area (long vertical black arrow) within the PTV45 area (short horizontal black arrow). Stars show rosacea in and outside treatment volumes. (B): Photo at 18 months post RT showing complete response of BCC but also complete and enduring response of rosacea both inside and outside the VMAT treatment volume.



**Figure 5** (Axial planning scan of case 1 with long white down arrows showing the wires defining the area of persisting rosacea and the short white up arrows showing the wires defining the area of complete response of rosacea. The pink volumes were contoured to compute maximum minimum and median doses to these volumes.

all cases showing that a dose less than 45Gy may work. The VMAT given for nose is essentially tangential VMAT<sup>[10]</sup>. There is a splay of dose into the surrounding skin. In order to quantify this, templates<sup>[15]</sup> were taken of cases 1, 3 and 4 and photos of case 2. These were used to capture the dimensions of the successfully treated areas. They were



**Figure 6** SXRT field for treating the remaining recalcitrant rosacea on right cheek in case 1. (A): SXRT field at planning. (B): SXRT field showing peak reaction. (C): 6 weeks after SXRT showing complete clearance of rosacea.

overlayed onto the planning scan to deduce the doses associated with durable rosacea control. This was also done for the areas of persisting rosacea in cases 1 and 2 more distant from the treatment area. See figure 5.

Maximum, minimum and mean doses were calculated. The calculation of mean dose is probably compromised by being too elevated in cases 1, 3 and 4 by the SIB approach. These are summarised in table 2.

**RT parameters for a prospective protocol of definitive RT for recalcitrant rosacea**

The cause of this study was the patient in case one who returned requesting definitive RT of persisting recalcitrant rosacea that was well outside the VMAT volume. How should she be treated? What are the radiotherapy parameters that are needed to treat successfully especially given that this is a benign disease? What would a prospective study look like?

**Volume**

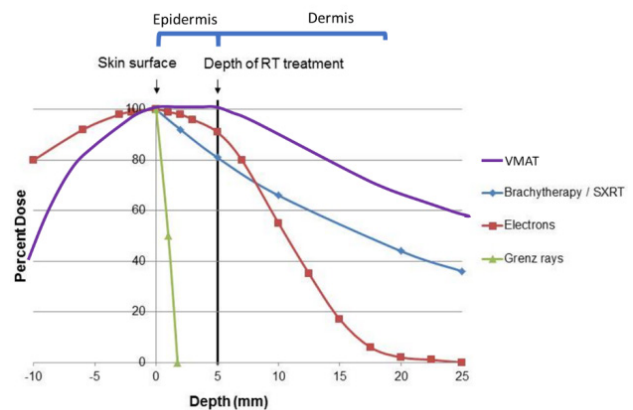
Our VMAT protocol<sup>[13]</sup> suggests a CTV 3-5mm thick encompassing the epidermis and dermis with a PTV expansion of 5mm into the overlying bolus and 2mm expansion into the dermis. From the success of this case series, this adequately covers the target. The target is probably epidermis and dermis including the pilo-sebaceous unit in the dermis colonised by the pathogenic Demodex mites and bacteria such as Staphylococcus epidermidis as described by Rivero *et al*<sup>[4]</sup>. Five millimetres will cover the depths of hair follicles and sweat glands<sup>[23]</sup>.

**Modality**

Rosacea covers the central face which has many convex undulations and so VMAT provides the best solution<sup>[11]</sup>. For flatter areas, such as the residual rosacea in case 1, or glabellar or perioral areas, other modalities could be used, such as superficial radiotherapy (SXRT) or megavoltage electrons as long as adequate dose was given to the target.

**Total dose**

A reasonable way forward based on the total dose discussion above is to use the VMAT nose dose for ESFC without SIB for invasive disease. This is 45 Gy in 25 fractions. This dose worked in 100% of our cases. This dose fits with the literature. As this is a benign disease there will be pressure to use a lower dose, as is used in other benign conditions<sup>[24,25]</sup>. However, to dose reduce initially and get a negative result may dampen enthusiasm to complete the study at the proper dose. The residual disease left in our cases and the literature review<sup>21</sup> shows that 6Gy is too low.



**Figure 7** Depth doses of different RT modalities in skin. VMAT gives a more homogenous dose throughout the target volume. Schematic only. This graph shows the depth doses of different RT modalities through the first few layers of skin. A thin black vertical line at zero represents the skin surface. Another thick black vertical line represents 5mm into tissue, the deepest point that skin appendages penetrate, so this area can be classed as the volume that contains the epidermis<sup>[23]</sup>. Megavoltage modalities (Purple line = volumetric modulated arc therapy [VMAT] and red line = electrons [MeV]) need build up (BU) or “bolus” to ensure full dose to the surface.

**Table 1** Patient and treatment details of the four cases.

Case	Sex/age	Duration of Rosacea (years)/ Invasive disease	VMAT SIBs to 55Gy	VMAT for field dose Total Gy/ No of Fractions/ Days per week	Continuing control of BCC and rosacea months)
1	F 73	15/BCC	3	45/25/5	18
2	F94	10/BCC	0	45/15/5	16
3	M 74	15/BCC	1	43.2/24/5	27
4	M72	8/BCC	1	45/25/5	25
Ave	78	12/BCC	1.5	45/22.25/5	21

Ave: Average; BCC: Basal Cell Carcinoma; F: Female; M: Male; Gy: Gray; SIB: Simultaneous Integrated boost; VMAT: Volumetric Modulated Arc Therapy.

**Dose per fraction**

In cases 1, 3 and 4 fractional doses of 1.8Gy and were associated with good infield rosacea control yet satisfactory late effects at a mean of 21 months. Lower dose per fraction would cause the patient to come for more rather than less visits to the radiotherapy department and would not achieve a better functional or cosmetic result in normal tissues on the limited data these 4 cases have given us. A higher dose per fraction may be associated with more long-term fibrosis in an area where a good functional and cosmesis is needed. Therefore hypofractionation should be discouraged and should only be considered if there are significant mobility issues about attending for the total number of fractions.

**Table 2** Dosimetry from the planning scans of these cases associated with durable control of rosacea.

Case	RT dose to area of controlled Rosacea (Gy)	Isodose line (Gy) associated with edge of rosacea control from overlay of template on RT plan	RT dose to area of not controlled rosacea (Gy)
1	max= 57; min = 35; mean= 45	35	max=24; min=2; mean=7
2	max= 47; min = 23; mean= 40	35	max=4.9; min=4.8; mean=4.8
3	max= 57; min = 34; mean= 43	38	NA
4	max= 56; min = 35; mean= 45	38	NA
Ave	max= 54; min = 32; mean= 44	36.5	Average of cases 1 and 2; 7+5/2=6

Ave: Average; Gy: Gray; Max: maximum; Min: minimum

**Use of a treatment break**

For benign and in situ disease a break can be inserted after 10 fractions with no detriment to treatment outcome<sup>[24,25,26]</sup>. A break of at least two weeks helps to decrease toxicity in normal skin<sup>[27]</sup> and therefore to complete the RT prescription in this usually elderly population.

**Consenting to RT for rosacea only - chance of second malignancy**

The radiation oncologist (RO) is required to obtain informed consent for radiation treatment from a requesting patient. In the case of rosacea only, with no invasive or in situ disease in field, the RO needs to obtain consent specifically for the rare chance of second malignancy arising as a result of the RT. All the cases in this study were being treated for cancer and only incidentally had a durable complete response to in-field rosacea. The risk of second malignancy from irradiation of the skin is approximately one cancer in one thousand patients irradiated every ten years<sup>[28]</sup>.

**Type of patient cohort for a prospective trial**

In designing a prospective phase 1/2 trial to establish the safety, efficacy and dose, it would be prudent to begin with older patients, eg over 60 years of age, as they will have more chance of having recalcitrant rosacea. Recalcitrant rosacea could be defined as patients who have suffered with rosacea for more than 10 years, have progressed through at least one topical and/or oral therapy, and are able to complete definitive RT for this condition. Older patients on average will have less time to develop a radiation induced malignancy. This study duration of follow up would only have to be for a year to be the longest study to date to look at outcome in rosacea<sup>[9]</sup>. Patient numbers needed will be low as there was no patient with rosacea who did not get a complete response at the dose prescribed, so perhaps cohorts of 8 would be enough. A Phase 3 trial is not needed as there is no known effective therapy to compare RT with.

**Design of a prospective trial**

Using the patient profile as defined above, the trial could consist of three cohorts of eight patients each. Cohort one gets 45/25 without a break, cohort two gets the same dose but with a two-week break after 13 fractions and the third cohort gets 13 fractions with the other 12 at relapse. This would test whether the break confers less acute effects for the same control. It would also test whether dose reduction is possible to half the dose level, without losing the opportunity of complete response with the completion of RT at salvage. Primary endpoint follow-up (FU) would be at one year following the start of RT, with a total FU of two years.

**Translational component**

The patients in the trial could also have biopsies taken pre and post RT. The biopsies could be three - one of in-field skin affected by rosacea, another of out-of-field skin from a sun exposed area but not

**Table 3** Comparison of disease control outcomes of these cases to the literature.

Study	Cases	Total dose (Gy)/fractions (Average)	Result
Plenk et al[20]	1 x Rhinophyma	40/16	PR at 9 years
	1 x Rhinophyma	39/11	PR at 7 years
Skala et al[21]	1 x Rhinophyma	40/20	PR at 7 years
Fairris et al[22]	9 palmoplantar pustulosis	(6/6)	5/6 relapsed in 6 weeks
This study	1 x Rhinophyma (case 3)	38/25	PR 27 months
This study	3 x rosacea (cases 1, 2, 4)	(36.5/25)	CR at average 23 months
This study	2 x persisting rosacea (cases 1, 2)	(6/20)	Persisting at 9 months

CR: Complete response; PR: partial response; Gy: Gray.

affected by rosacea, perhaps close to the rosacea area, and a third from out-of-field skin from a non - sun exposed area eg axilla. These could be done pre-RT and at one year post RT.

**Case 1 Further treatment for remaining recalcitrant rosacea**

Bearing in mind the above considerations, Case 1 was treated to the area outlined in Figure 6. She was treated with a superficial radiotherapy technique (SXRT) using a Xstrahl 300 machine to dose of 40Gy in 20 fractions five times a week with a planned break of two weeks after 10 fractions as a way of decreasing acute side effects. She had minimal acute toxicity and complete resolution of her remaining rosacea at four weeks post treatment.

When this patient was asked five months later which modality gave her the best clearance of rosacea, she volunteered that the VMAT was superior. This was despite the VMAT causing more toxicity as it was to a higher dose, given without a break and causing mucositis from exit beam going through to the nasal mucosa. This subjective better clearance may be because VMAT gives a more homogenous dose throughout the target volume. See Figure 7.

**CONCLUSION**

Rosacea is a common chronic illness with no known durable cure. We present 4 cases of incidental long-term control of recalcitrant rosacea following definitive VMAT radiotherapy for BCC amongst ESFC. At last follow up at an average of 21 months post RT, all cases had continuing complete response of the BCC and ESFC but also had enduring complete response of rosacea within and immediately outside the prescribed RT area. The durability of rosacea control was associated with target volumes at least receiving an average of 36.5 Gy in an average of 22.5 fractions. The natural progression is to a prospective study and the cases and a literature review were used to define parameters for a protocol. This proposed study will investigate in a prospective way whether RT can provide the durable cure needed. Trial patients with recalcitrant rosacea are defined as



those who have suffered with rosacea for more than 10 years, have progressed through at least one topical and/or oral therapy. Only those able to complete definitive RT for this condition should be included in a trial.

The trial parameters include the target volume which is a CTV encompassing the epidermis and dermis which includes the pilosebaceous unit colonised by the pathogenic Demodex mites and bacteria such as Staphylococcus epidermidis, thought to be the causative agents. The best modality to cover the undulating central face is VMAT. Other modalities can be used for flatter areas. Total dose is 45 Gy in 25 fractions which also fits with the literature. This was associated with good infield rosacea control yet satisfactory late effects at a mean of 21 months in our study. In this benign disease a break can be inserted after 13 fractions and helps to decrease toxicity and therefore to complete RT with no detriment to treatment outcome. Consent should include the rare chance of RT induced malignancy. The type of patient cohort for a prospective trial would be with older patients, eg over 60 years of age, as they will have a longer history of recalcitrant rosacea.

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## REFERENCES

- Spoendlin J, Voegel JJ, Jick SS et al. A study on the epidemiology of rosacea in the U.K. *Br J Dermatol* 2012; **167**: 598-605. [PMID: 22564022]; [DOI: 10.1111/j.1365-2133.2012.11037.x]
- Chang ALS, Raber I, Xu J et al. Assessment of the genetic basis of rosacea by genome-wide association study. *J Invest Dermatol* 2015; **135**: 1548-55. [PMID: 25695682]; [DOI: 10.1038/jid.2015.53]
- Tüzün Y, Wolf R, Kutlubay Z, Karakuş O, Engin B. Rosacea and rhinophyma. *Clin Dermatol*. 2014 Jan-Feb; **32**(1): 35-46. [PMID: 24314376]; [DOI: 10.1016/j.clindermatol.2013.05.024.]
- Rivero AL, Whitfield M. An update on the treatment of rosacea. *Aust Prescr*. 2018; **41**(1): 20-24. [DOI: 10.18773/austprescr.2018.004]
- Zeichner JA, Eichenfield LF, Feldman SR, Kasteler JS, Ferrusi IL. Quality of Life in Individuals with Erythematotelangiectatic and Papulopustular Rosacea: Findings From a Web-based Survey. *J Clin Aesthet Dermatol*. 2018; **11**(2): 47-52. [PMID: 29552276]; [PMCID: PMC5843362]
- Engin B, Özkoca D, Kutlubay Z, Serdaroğlu S. Conventional and Novel Treatment Modalities in Rosacea. *Clin Cosmet Investig Dermatol*. 2020; **13**: 179-186. [PMID: 32110082]; [DOI: 10.2147/CCID.S194074]
- Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part II. Topical and systemic therapies in the treatment of rosacea. *J Am Acad Dermatol* 2015; **72**: 761-70. [PMID: 25890456]; [DOI: 10.1016/j.jaad.2014.08.027]
- Del Rosso JQ, Tangheiti E, Webster G, Stein Gold L, Thiboutot D, Gallo RL. Update on the Management of Rosacea from the American Acne & Rosacea Society (AARS). *J Clin Aesthet Dermatol*. 2019; **12**(6): 17-24. [PMID: 31360284]; [PMCID: PMC6624012]
- van Zuuren, EJ; Fedorowicz, Z (September 2015). Interventions for rosacea: abridged updated Cochrane systematic review including GRADE assessments. *The British Journal of Dermatology*. **173** (3): 651-62. [PMID: 26099423]; [DOI: 10.1111/bjd.13956]
- E. Daniel Santos, Julia A. Green, Nastik Bhandari, Angela Hong, Pascale Guitera, Gerald B. Fogarty. Tangential Volumetric Modulated Radiotherapy - A New Technique for Large Scalp Lesions with a Case Study in Lentigo Maligna. *INT. J. BIOAUTOMATION*, 2015, **19**(2): 223-236
- Fogarty GB, Christie D, Spelman LJ, Supranowicz MJ, Sinclair RS. Can Modern Radiotherapy be used for Extensive Skin Field Cancerisation: An Update on Current Treatment Options. *Biomed J Sci & Tech Res* **4**(1)- 2018. BJSTR.MS.ID.000998. [DOI: 10.26717/BJSTR.2018.04.000998.]
- Martin TD, Moutrie Z, Tighe D, et al. Volumetric modulated arc therapy (VMAT) for skin field cancerisation of the nose - A technique and case report. *Int J Radiol Radiat Ther*. 2018; **5**(3): 142-148. [DOI: 10.15406/ijrrt.2018.05.00152]http://medcraveonline.com/IJRRT/IJRRT-05-00152.pdf
- Potter A, Price M, Papworth D, et al. A technique for treating extended skin field cancerisation using volumetric modulated arc therapy. *Int J Radiol Radiat Ther*. 2019; **6**(4): 111-119. [DOI: 10.15406/ijrrt.2019.06.00230] https://medcraveonline.com/IJRRT/IJRRT-06-00230.pdf
- T. Landberg, J. Chavaudra, J. Dobbs, G. Hanks, K.-A. Johansson, T. Möller, J. Purdy, Report 50, Journal of the International Commission on Radiation Units and Measurements, Volume os26, Issue 1, 1 September 1993.[DOI: https://doi.org/10.1093/jicru/os26.1.Report50]
- Alcevski B, Shearer T, Yeong Y, et al. Techniques to verify the correct skin areas for biopsy, treatment, recurrence and in-vivo dosimetry using an A4 plastic sheet as template. *Int J Radiol Radiat Ther*. 2020; **7**(4): 112-118. [DOI: 10.15406/ijrrt.2020.07.00275]
- Wong B, Christie D, Hellyer J, et al. Volumetric modulated arc therapy (VMAT) for extensive skin field cancerisation (ESFC) - exploring the limits of treatment volumes with a case series of backs. *Int J Radiol Radiat Ther*. 2020; **7**(6): 184-192. [DOI: 10.15406/ijrrt.2020.07.00286]
- Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors. *J Am Acad Dermatol* 2015; **72**: 749-58. [PMID: 25890455]; [DOI: 10.1016/j.jaad.2014.08.028]
- Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. *Exp Dermatol* 2017; **26**: 659-67. [PMID: 27376863]; [DOI: 10.1111/exd.13143]
- Datta I, Casanas B, Vincent AL, Greene JN. The red face: Erysipelas versus Parvovirus B19, SLE, and Rosacea. *Asian Biomed*. 2010 Feb 18; **3**(6): 681-8. [DOI: 10.5372/ABM.V3I6.273]
- Plenk HP. Rhinophyma, associated with carcinoma, treated successfully with radiation. *Plast Reconstr Surg* 1995. [PMID: 7870783]; [DOI: 10.1097/00006534-199503000-00020]
- Skala M, Delaney G, Towell V, Vladica N. Rhinophyma treated with kilovoltage photons. *Australas J Dermatol*. 2005; **46**(2): 88-89. [PMID: 15842400]; [DOI: 10.1111/j.1440-0960.2005.00148.x]
- Fairris GM, Jones DH, Mack DP, Rowell NR. Superficial X-ray therapy in the treatment of palmoplantar pustulosis. *British Journal of Dermatology*. 1984 Oct; **111**(4): 499a-500. [PMID: 6386035]; [DOI: 10.1111/j.1365-2133.1984.tb06616.x]
- Fogarty, G. B., A. Hong, R. A. Scolyer, E. Lin, L. Haydu, P. Guitera, and J. Thompson. "Radiotherapy for lentigo maligna: a literature review and recommendations for treatment." *British Journal of Dermatology* 170, no. **1** (2014): 52-58. [PMID: 24032599]; [DOI: 10.1111/bjd.12611]
- Seegenschmiedt MH, Olschewski T, Guntrum F, "Radiotherapy optimization in early-stage Dupuytren's contracture: first results of a randomized clinical study", *Int J Radiat Oncol Biol Phys*. **49/3** (2001) p 785-798. [PMID: 11172962]; [DOI: 10.1016/s0360-3016(00)00745-8]

25. Betz N, Ott OJ, Adamietz B *et al.* Radiotherapy in Early-stage Dupuytren's Contracture. Long-term results after 13 years. *Strahlentherapie und Onkologie* 2010; **186**: 82-89 [PMID: 20127225]; [DOI: 10.1007/s00066-010-2063-z]
26. Gerald B Fogarty, Joanne Sullivan, Tina Gorjiara, Leslene Diedericks, Keng-Ee Thai. Split Course Superficial Radiotherapy in Scrotal Extramammary Paget's Disease Allows Course Completion With Minimal Side Effects: A Case Study. *J. of Dermatological Res.* 2020 April; **5(1)**: 202-205. ISSN 2413-8223. [DOI: 10.17554/j.issn.2413-8223.2020.05.53] <http://www.ghrnet.org/index.php/jdr/article/view/2886/3171>
27. Fogarty GB, Christie DRH, Kaminski A, *et al.* A radiation oncology approach for using definitive radiotherapy with volumetric modulated arc therapy (VMAT) for skin field cancerisation (SFC). *Int J Radiol Radiat Ther.* 2018; **5(4)**: 227-234. [DOI: 10.15406/ijrt.2018.05.00168]
28. Fogarty GB, Shumack S. Common dermatology questions and answers about the radiation treatment of skin cancer in the modern era. *Int J Radiol Radiat Ther.* 2018; **5(2)**: 108-114. [DOI: 10.15406/ijrt.2018.05.00145]