European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-020-05088-z

ORIGINAL ARTICLE

High dose brachytherapy with non sealed ^{188}Re (rhenium) resin in patients with non-melanoma skin cancers (NMSCs): single center preliminary results.

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Received: 17 August 2020 / Accepted: 20 October 2020

Abstract

Background and aim High dose brachytherapy using a non sealed ^{188}Re-resin (Rhenium-SCT®, Oncobeta® GmbH, Munich, Germany) is a treatment option for non-melanoma skin cancer (NMSC). The aim of this prospective study was to assess the efficacy and the safety of a single application of Rhenium-SCT® in NMSC.

Materials and method Fifty consecutive patients (15F, 35 M, range of age 56–97, mean 81) showing 60 histologically proven NMSCs were enrolled and treated with the Rhenium-SCT® between October 2017 and January 2020. Lesions were located on the face, ears, nose or scalp ($n = 46$), extremities ($n = 9$), and trunk ($n = 5$). Mean surface areas were 7.0 cm^2 (1–36 cm^2), mean thickness invasion was 1.1 mm (0.2–2.5 mm), and mean treatment time was 79 min (21–85 min). Superficial, mean, and target absorbed dose were 185 Gy, 63 Gy, and 31 Gy respectively. Patients were followed-up at 14, 30, 60, 90, and 180 days posttreatment, when dermoscopy and biopsy were performed. Mean follow-up was 20 months (range 3–33 months). Early skin toxicity was classified according to Common Terminology Criteria for Adverse Events (CTCAE). Cosmetic results were evaluated after at least 12 months according to Radiation Therapy Oncology Group (RTOG) scale.

Results At 6 months follow-up, histology and dermoscopy were available for 54/60 lesions, of which 53/54 (98%) completely responded. One patient showed a 1-cm^2 residual lesion that was subsequently surgically excised. Twelve months after treatment, 41/41 evaluable lesions were free from relapse. Twenty four months after treatment, 23/24 evaluable lesions were free of relapse. In 56/60 lesions early side effects, resolving within 32 days were classified as grades 1–2 (CTCAE). In the remaining 4/60 lesions, these findings were classified as grade 3 (CTCAE) and lasted up to 8–12 weeks but all resolved within 90 days. After at least 12 months (12–33 months), cosmetic results were excellent (30 lesions) or good (11 lesions).

Conclusion High dose brachytherapy with Rhenium-SCT® is a noninvasive, reasonably safe, easy to perform, effective and well-tolerated approach to treat NMSCs, and it seems to be a useful alternative option when surgery or radiation therapy are difficult to perform or not recommended. In our population 98% of the treated lesions resolved completely after a single application and only one relapsed after 2 years. Larger patients' population and longer follow-up are needed to confirm these preliminary data and to find the optimal dose to administer in order to achieve complete response without significant side effects.

Keywords Non-melanoma skin cancers · Brachytherapy · ^{188}Rhenium · Not- sealed sources

This article is part of the Topical Collection on Oncology - General.

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Published online: 02 November 2020

Introduction

Non-melanoma skin cancers (NMSCs) are the most common cancers in humans and represent about 80% of all skin cancer cases, with more than 3 million patients treated every year. [1] Basal cell carcinoma (BCC) is the most frequent NMSC, accounting for 70% of cases, while squamous cell carcinoma (SCC) accounts for 20%, although its incidence is rising.

Risk factors for NMCSs are: fair skin phototype, chronic sun exposure, old age, immunosuppression, and HPV infection.

Most NMSCs are located on areas more exposed to sun light, in particular, the scalp, face, and hand dorsum [1].

The treatment of choice is in most cases surgery. Mohs micrographic surgery (MMS) is currently considered the best option for primary NMSC demonstrating a 5-year cure rate higher than 95% in both BCCs [2] and SCCs [3]. However, the main limitation to MMS is represented by patients with large or multiple lesions localized in areas where radical surgical approach is technically difficult or disfiguring. These may include the nose-wing, ears, eyelids, lips, external genitals, or fingers. In these cases, the results of surgery may be suboptimal in terms of radicality and cosmetic results, while also reducing the functionality of the treated areas [4].

For elderly patients, the choice of therapy also depends on the patient general health condition, mental health, life expectancy, and personal preference; therefore, treatment modalities other than surgery should be carefully considered. Nonsurgical treatment options of NMSCs include cryo-therapy, topical medication such as imiquimod and 5-fluorouracil, photodynamic therapy, curettage and electrodessication, laser-therapy, and electronic brachytherapy [4].

Electronic brachytherapy with sealed solid sources is an alternative method that showed excellent results. Its limitation is mainly due to the difficulty to treat large lesions or lesions with nonplanar concave or convex surfaces (the nose, ears, lips, external genitals) [5].

High dose brachytherapy using a nonsealed rhenium-188 resin, commercially known as Rhenium-SCT® (Oncobeta® GmbH, Munich, Germany), is a new treatment option that makes it possible to bring radioactivity as close as possible to the whole surface of the lesion independently of its three-dimensional shape and size.

This brachytherapy technique is based on the property of ^{188}Re to release a high energy, emitting 85% beta and 15% gamma radiation (Beta 2.2 MeV; Gamma 155KeV).^{188}rhenium releases 92% of its energy within 2-mm depth in the skin. [6]

Brachytherapy with ^{188}Re may have a clinical role as a tailored treatment in cases where (a) surgery or EBRT or other brachytherapy approaches would be suboptimal with regard to the location, the extent of the lesion or the cosmetic outcome that may result from skin surgery; (b) patients would not be eligible for surgery considering their general health condition and comorbidities; and (c) patients who refuse surgery. The limited literature on this subject does not allow for a systematic analysis of the results of this method, which however appears to be very promising and to date has provided excellent results in terms of long-term outcome and absence of significant long-term side effects [7–10].

We present the preliminary results of our first experience (from October 2017 to January 2020) on the use of this technique in a population of patients affected by NMSCs. The main goal was to assess the clinical efficacy and safety of a single application of a standardized high dose brachytherapy using a nonsealed ^{188}Re source in the treatment of NMSCs.

Material and methods

The study was performed according to the Helsinki Declaration, patients signed written informed consent to participate, and the study was approved by local Ethical Committee (23/2019/Oss/AOUBo). Between October 2017 and January 2020, patients affected by NMSC (including both new diagnosis and relapses) were selected by the Dermatology Unit of the Azienda Ospedaliero-Univarsitaria of Bologna, S. Orsola–Malpighi Hospital.

Inclusion criteria of our study were (1) histologically proven cutaneous BCC or SCC; (2) lesion thickness invasion not deeper than 2.5 mm (arbitrary cutoff based on ^{188}Re characteristics) according to single or multiple diagnostic biopsies; (3) lesions located in the scalp, face, ears, or fingers or other areas in which surgery, EBRT or standard brachytherapy would have been difficult to perform; and (4) contraindication or refusal of surgery.

Population characteristics

Between October 2017 and January 2020, 50 consecutive patients (15F, 35 M, range of age 56–93 years; mean 81) showing 60 histologically proven NMSCs (41BCC; 18SCC; 1BCC&SCC) were enrolled. Lesions were located on the face, ears, nose or scalp (46), extremities (9), and trunk (5). Mean surface area was 7.0 cm^2 (range 1–36 cm^2) and mean thickness invasion 1.1 mm (range 0.2–2.5 mm). Mean treatment time was 79 min (range 21–285 min). In our population, 18 out of 60 lesions had already been treated with other therapies and relapsed (five lesions had already received surgery; two lesions surgery and photodynamic therapy or cryotherapy; ten lesions had already received cryo-therapy, laser and photodynamic therapy; one imiquimod) while 42 lesions were new diagnoses at presentation.

Table 1 Patient population

Population details			
Patients		Lesions	
Num. of patients	50	Num. of NMSCs lesions	60
Age (years)—mean and range	81 (56–97)	BCC	41 (70%)
M/F	35/15	SCC	18 (25%)
Follow-up (months)—mean and range	18 (3–30)	BCC and SCC	1 (2%)
Localization		Lesions characteristics	
Head (face and scalp)	46 (76%)	Surface area (cm^2) mean (range)	7.0 (1–36)
Extremities 9 (15%)		Thickness invasion (mm) mean (range)	1.1 (0.2–2.5)
		Volume (cm^3) mean (range)	0.7 (0.05–7.2)
Trunk	5 (9%)	Previously treated	18 (33%)
^{188} Re Administered	Mean 335 MBq (range 48–1028)	Treatment time	Mean 78 min (range 21–285)

NMSC nonmelanoma skin cancer; *BCC* basal cell carcinoma; *SCC* squamous cell carcinoma

Patients' characteristics are reported in Table 1.

Follow-up

Patients were followed-up after 14–30–60–90–180 days from the treatment and then every 90–180 days up to 33 months.

Standard of reference

Six months after Rhenium-SCT® treatment, patients were classified as complete responders (CR) if the dermoscopy did not show any suspected area of persistence of the disease that may deserve a biopsy or if the biopsy guided by the dermoscopy resulted negative; partial responders (PR) if the biopsy on a suspected area resulted positive but the treatment with Rhenium-SCT® caused a significant reduction in the extent of the lesion making possible the surgical excision or other local therapies with subsequent complete histological response; nonresponders (NR) in case of disease persistence.

Skin toxicity and cosmetic results

Two expert clinicians have classified early skin toxicity: a dermatologist (F.S.) and a radiation oncologist (A.G.M.). Early skin toxicity has been evaluated according to Common Terminology Criteria for Adverse Events (CTCAE 5.0) [11] within the first 30 days in all 60 lesions (Table 2). Cosmetic results have been evaluated after at least 12 months (range 12–33 months) in 41 evaluable lesions according to Radiation Therapy Oncology Group criteria (RTOG) [12] (Table 3).

Therapy details

The treatment consisted in a ^{188}Re-based resin application using a dedicated device (Rhenium-SCT®, Skin Cancer Therapy, Oncobeta® GmbH, Germany) provided with a carpoule filled with radioactive ^{188}Re resin. The radioactive resin is applied over a 7-μm foil placed over the skin lesion to avoid any direct contact of the resin with the skin.

The steps required for patient preparation, administration of therapy, and patient discharge and follow-up are summarized in Fig. 1.

The treatment goal was to deliver an adjusted normalized adsorbed dose to each single lesion to the deepest point of neoplastic infiltration (target dose) assessed by one or multiple pre-treatment biopsies in order to avoid retreatments. Calculation of the estimated dose on a single lesion has been performed using two independent methods: Varskin5 software [13] and the Monte Carlo Code Fluka [14]. Both methods allow assessing the dose distribution taking into account the energy spectrum of ^{188}Re, the thickness of the invasion, the surface of the lesion, the activity dispensed, and the duration of the treatment. In all the cases considered, the two methods result to be consistent.

In accordance with the previously reported data [7–10], the first 10 treated lesions were treated with an empiric mean target dose of 47 Gy to the deepest point of neoplastic invasion. Consequently, this resulted in a mean adsorbed dose to the whole volume of the lesion (mean dose) of 92 Gy and in a mean adsorbed dose at 0.01 mm of neoplastic invasion (superficial dose) of 260 Gy. Given the excellent response rate, but the not negligible incidence of early side-effects (see the "Results" paragraph), we proceeded to a progressive reduction of the delivered doses, we established a dose deescalation protocol using the target dose and the mean dose as indicators.

Table 2 Skin toxicity according to CTCAE 5.0 [11]

Skin Toxicity	G1	G2	G3	G4	G5
Atrophy	Mild	Marked			
Alopecia	< 50%	> 50%			
Pigmentation change	Mild or localized	Marked or generalized			
Erythema	Mild	Moderate	Severe	Necrosis	Death
Skin ulceration	< 1 cm	1–2 cm	> 2 cm	Deep structures involved	Death

Summarizing, the mean values of the adsorbed doses delivered were ten lesions received a target dose of 47 Gy, a mean dose of 92 Gy, and a superficial dose of 260 Gy; twenty-three lesions received a target dose of 35 Gy, a mean dose of 65 Gy, and a superficial dose of 185 Gy (25% reduction); twenty-seven lesions received a target dose of 23 Gy, a mean dose of 48 Gy, and a superficial dose of 155 Gy (50% reduction). See Table 4.

Treatment monitoring

According to our study design, patients were treated with Rhenium-SCT® on day 0 and followed by a dermatological examination on days 14, 30, 60, 90, 180, then every 90–180 days. The response to therapy was evaluated after 6 months, through clinical evaluation and dermoscopy examination, using both manual polarized noncontact dermoscopy (DermLite 3 Gen, San Juan Capistrano, California, USA) and digital nonpolarized contact dermoscopy (Foto Finder dermatoscope®, Teachscreen Software, Bad Birnbach, Germany) followed by a biopsy (if clinically needed).

Statistical analysis

Univariate and multivariate analysis of the predictive factors of CTCAE G3 acute toxicity was performed using the logistic regression model including all the dosimetric (e.g., target dose, mean dose, superficial dose) and lesion related variables (e.g., treated areas) as continuous, variables. The utility of the identified variables as early predictor of toxicity has been assessed using the area under curve (AUC) of ROC curve. When a perfect correlation of predicted versus observed toxicity was found, the AUC was equal to 1 whereas random assignment of outcome led to a ROC/AUC of 0.5 [15]. The data analysis was performed with R version 3.6.3 [16].

Results

Six months after Rhenium-SCT® treatment, 54 evaluable lesions have been studied with dermoscopy and/or histology after biopsy. In 49/54 lesions, a dermoscopy followed by a biopsy have been performed while in 5/54 dermoscopy did not show any suspicious finding that could guide to a biopsy, therefore the biopsy was not performed. According to these diagnostic tests, 53 out of 54 lesions (98%) completely responded (CR) to Rhenium-SCT® regardless of the dose received. Only a 91-year-old female patient presenting a 9.5-cm^2 BCC (0.6-mm thickness) in the nose pyramid and left nose wing showed a small persistence of disease (patient classified as PR). This patient showed a suspicious area of persistent disease at dermoscopy, and the subsequent biopsy confirmed the presence of a small (1 cm^2) basal cell carcinoma persistence located in the center of the field of irradiation. This lesion was surgically treated with a subsequent complete response and good cosmetic results. Twelve months after treatment, all the 41/41 evaluable lesions were free from relapse at dermoscopy. Twenty-four months after treatment 23/24 evaluable lesions were free of relapse while one patient treated for a 11.4-cm^2 BCC (0.4-mm thickness) in the scalp showed a

Table 3 Cosmetic scale according to RTOG [12]

Cosmetic scale	Definition
Excellent	No changes, to slight atrophy or pigment change, or slight hair loss or no changes to slight induration or loss of subcutaneous fat
Good	Patch atrophy, moderate telangiectasia, and total hair loss; moderate fibrosis but asymptomatic; slight field contracture with less than 10% linear reduction
Fair	Marked atrophy and gross telangiectasia; severe induration or loss of subcutaneous tissue, field contracture greater than 10% linear measurement
Poor	Ulceration or necrosis

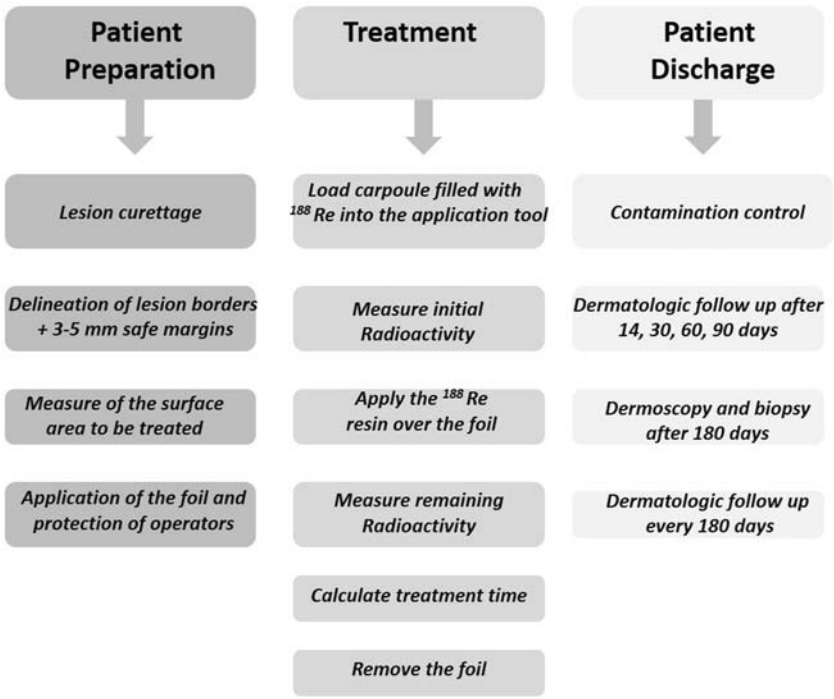

Fig. 1 Patient's preparation, patient's treatment and patient's discharge and follow-up

small (< 1 cm^2) relapse in the edge of the field of irradiation. We scheduled this patient for a retreatment.

Side effects

Different grades of early skin localized side effects started approximately after 14 days in all lesions and resolved completely within 90 days with excellent/good cosmetic results after 12–33 months. None of the patients reported significant pain or discomfort during or after the procedure. None of the patients showed any significant late side effect except dyschromia or slight atrophy of the skin or hair loss. None of the patients showed any significant late side effect during the follow-up period (3–33 months). Overall results, skin toxicity, cosmetic results, and follow-up are reported in Table 5.

In 56/60 lesions, early side effects, resolving within 32 days (mean 4 weeks), were consistent with skin erythema, faint or moderate edema, or little ulcerations (grades 1–2). In the remaining 4/60 lesions, these findings were more severe (grade 3) lasted up to 8–12 weeks (mean 10 weeks), but resolved within 90 days in all the cases. It is interesting to point out that two of

Table 4 Lesions characteristics of the three dose de-escalation groups based on the adsorbed Target Dose

Target dose * Mean dose** Superficial dose*** Deescalation	Number of treated lesions	Treated surface area (cm^2)	Neoplastic thickness invasion (mm)	Volume (cm^3)
47 Gy (target dose) 92 Gy (mean dose) 260 Gy (superficial dose)	10	5.8	1.1	0,7
35 Gy (target dose) 66 Gy (mean dose) 185 Gy (superficial dose) 25% deescalation	23	5.3	0.9	0,4
23 Gy (target dose) 48 Gy (mean dose) 155 Gy (superficial dose) 50% deescalation	27	9.0	1.2	1,0

*Target dose: adsorbed dose to the deepest point of neoplastic invasion. **Mean dose: adsorbed dose by the whole volume of the lesion. ***Superficial dose: adsorbed dose at 0.01 mm of neoplastic invasion

Table 5 Overall results in the three groups of dose deescalation based on the target dose defined as the adsorbed dose to the deepest point of neoplastic invasion. Acute skin toxicity according to CTCAE 5.0 [10]. Cosmesis according to RTOG cosmetic scale [11]. Follow-up according to dermatologic examination and dermoscopy

Variables	Target dose 23 Gy ($n = 27$)	Target dose 35 Gy ($n = 23$)	Target dose 47 Gy ($n = 10$)	Total n 60 (100%)
Efifcacy Re SCT	21	23	10	54
CR	21	22	10	53 (98.2%)
PR	/	1	/	1 (1.8%)
Acute skin toxicity				60
G1	15	12	4	31 (51.6%)
G2	10	11	4	25 (41.6%)
G3	2	/	2	4 (6.6%)
Cosmesis (RTOG)				41
Good	4	3	4	11 (26.8%)
Excellent	5	19	6	30 (73.1%)
Follow-up				
12 months				41
CR	9	22	10	
Relapse	/	/	/	
24 months				24
CR	1	12	10	
Relapse		1		

these four lesions were located in the legs while the remaining two in the ear and face. Cosmetic results were evaluated in 41/60 evaluable lesions after a period of 12–33 months according to RTOG Cosmetic scale [12]. Thirty lesions were classified as excellent and 11 lesions as good.

The characteristics of these lesions are reported in Table 6.

Predictors of acute toxicity

Multivariate logistic regression analysis showed that both the mean dose and the treated surface areas were significantly and independently related to G3 acute toxicity. The AUC resulted 0.830 (p value = 0.0103) indicating that the mean dose and the treated surface areas are reliable predictors of toxicity. Univariate and multivariate logistic regression analysis are reported in Table 7.

Discussion

The few papers published so far on the use of nonsealed brachytherapy with ^{188}Re source in NMSC have shown very interesting results: Sedda et al. [7] treated 53 patients with NMSC with an acrylic ^{188}Re matrix. In all cases, clinical remission occurred after 3 months while complete healing was obtained in 82% of the cases without any significant long-term side effect. The remaining 18% of patients required multiple applications. After a follow-up of 20–72 months, no clinical relapses were observed, and histology confirmed complete response in all cases. Authors did not report data about early or late toxicity. Carrozzo et al. [8] treated 15 patients with a histologically confirmed diagnosis of squamous cell cancer of the penis (SCCP). In this population, 12 healed, and two patients did not respond to ^{188}Re brachytherapy. It is worth to underline that in these studies Authors delivered a standard

Table 6 Comparison of G1–2 vs G3, early toxicity, lesions characteristic's, and dose received

Early toxicity (CTCAE 5.0)	Duration early toxicity (weeks)	Cosmetic results (41 lesions)	Treated surface area (cm^2)	Neoplastic thickness invasion (mm)	Volume (cm^3)	Superficial dose * (Gy)	Mean dose ** (Gy)	Target dose *** (Gy)
56 lesions Grades 1–2	4 weeks	10 good 27 excellent	6.4	1.0	0.6	180	62	31
4 lesions Grade 3	10 weeks	3 good 1 excellent	15.8	1,6	2,9	250	76	33

Early toxicity measured according to CTCAE 5.0 [10]; Cosmetic results measured after 12–33 months according to Cosmetic scale RTOG [11]. *Superficial dose: adsorbed dose at 0.01 mm of neoplastic invasion. **Mean dose: adsorbed dose by the whole volume of the lesion. *** Target dose: adsorbed dose to the deepest point of neoplastic invasion. To note the significantly difference in treated surface area between the two groups

Table 7 Univariate and multivariate logistic regression analysis of G1–G2 vs G3 toxicity according to CTCAE [10]

Univariate analysis	Variable	Coefficient	Standard error	*p* value
	Superficial dose * (Gy)	0.0053	0.0044	0.228
	Mean dose ** (Gy)	0.0232	0.0206	0.261
	Target dose to the deepest point of neoplastic invasion (Gy)	0.0172	0.0526	0.743
	Treated surface areas (cm2)	0.1187	0.0547	0.030
	Thickness neoplastic invasion (mm)	1.5165	0.9652	0.116
	Lesion volume (cm3)	0.8713	0.3834	0.023
Multivariate analysis §	Variable	Coefficient	Standard error	*p* value
	Treated surface areas (cm2)	0.2016	0.0759	0.0079
	Mean dose ** (Gy)	0.0545	0.0269	0.0426

§ $p = 0.0021$

Variables were superficial maximal dose (Gy), mean dose (Gy), treated surface areas (cm^2), thickness of neoplastic invasion (mm). In multivariate analysis only statistically significant variables are reported. *Superficial maximal dose: adsorbed dose at 0.01 mm of neoplastic invasion. **Mean dose: adsorbed dose by the whole volume of the lesion

dose of 50 Gy at the depth of 0.5 mm. This dosimetry was independent from the size and thickness of the lesions. Using this not personalized approach, the risk is to overtreat thin lesions and undertreat more thick lesions who may later deserve further treatments. Cipriani et al. [9] recently published a retrospective study on 52 patients showing 53 NMSC lesions and 2 extramammary Paget's disease, treated with Rhenium-SCT®. In this study, authors delivered a standard dose of 50Gy at the deepest point of neoplastic invasion that ranged from 0.3 to 0.6 mm. Authors do not report data about early skin toxicity or cosmetic results, however long-term results showed a complete clinical remission in 36 lesions after 6 months and in 19 lesions after at least 12 months. This data confirm the already reported promising results published by the same authors [10].

Our preliminary findings confirm the promising results reported by the few works published so far**.** Histological specimens or dermoscopy, performed 6 months after treatment showed a complete remission in all 54 studied lesions except one in which, however, Rhenium-SCT® treatment reduced significantly the size of the lesion and made possible surgery with a subsequent complete response. Only one patient showed a small relapse in the edge of the field of irradiation in the scalp after 24 months.

In our study, we administered a standardized adsorbed dose to the deepest point of neoplastic invasion (target dose) and to the whole volume of the lesion (mean dose) in order to find optimal standard adsorbed dose able to treat the lesion in one single application, avoiding severe early, and late side effects. Given the not negligible incidence of early side-effects during our preliminary experience, we proceeded to a progressive reduction of the delivered dose after the treatment of the first 10 lesions where we observed a 20% G3 toxicity according to CTCAE 5.0. We established a dose deescalation protocol. The early toxicity reduced in the other two groups of dose deescalation (Tables 5 and 6).

Overall, in our population, the incidence of acute toxicity, classified as G3, is low but not negligible, 4/60 (6.6%). A possible explanation of such relatively high quote of G3 early toxicity may lie on the fact that we enrolled patients with very large lesions in terms of treated surface area and volume if compared with the lesions commonly treated with high dose brachytherapy [17–19]. Moreover, we administered the dose in a single fraction.

However, it should be noted that all side effects were in most cases easily manageable, of short duration and not associated with pain, therefore without significant impact on patients' quality of life (Figs. 2, 3, 4, and 5). Even in the four lesions showing a severe early and "long lasting" toxicity, we observed a complete healing of the wound within a maximum of 90 days. In one of these patients (Fig. 2), we observed a complete healing with excellent cosmetic results after 12 months. The reason of such phenomenon may lie in the fact that beta radiations deliver more than 90% of their energy in the first 2 mm of the skin in the epidermis, without deeper involvement of the derma making possible a fast recovering of the wound [6].

A rigorous statistical analysis of our data seems premature, and it is not in the aim of this preliminary publication. However at multivariate logistic regression analysis, the treated surface area and the mean dose received by the lesions are the variables associated with the presence of severe (G3) early side effects. We have also observed early G3 toxicity in 2/4 patients showing lesions in the legs. This confirms the findings of Ballester-Sánchez et al. [19] in BCC patients treated with electronic brachytherapy. In their population, authors found that one of the statistically significant predictors of toxicity was the location of the lesion in trunk or extremities. We cannot draw any conclusions based only on these few

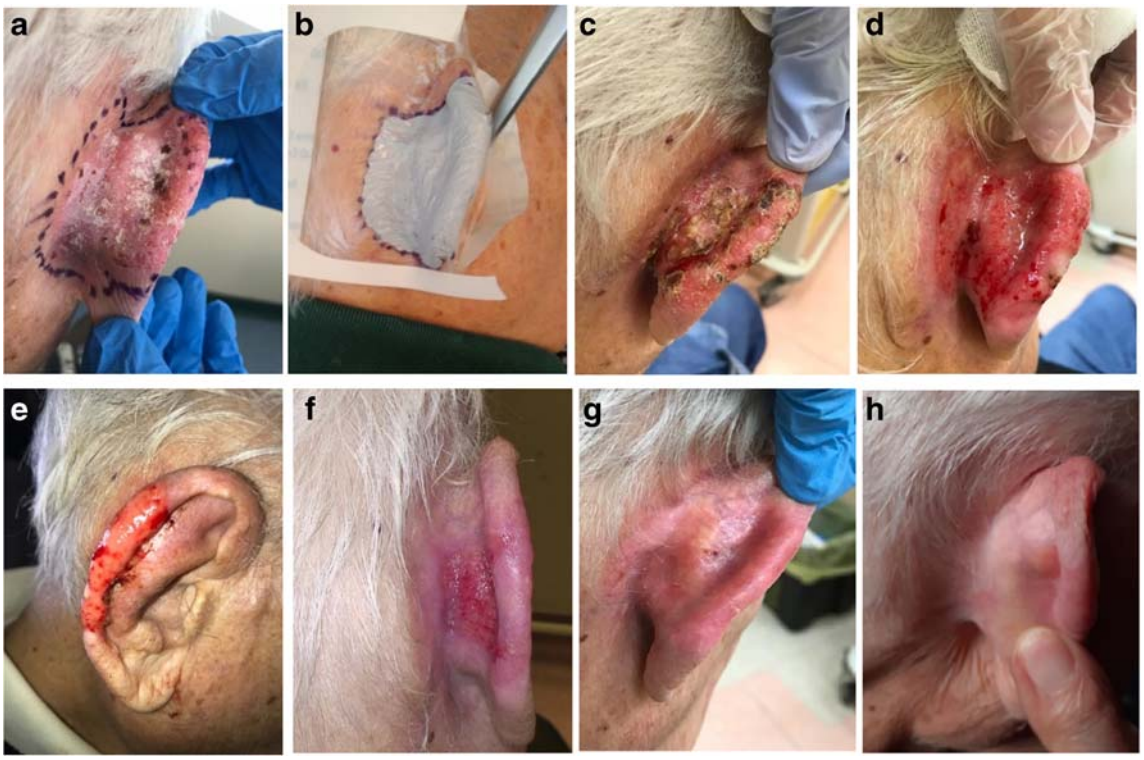

Fig. 2 Male 93 years old with SCC of the right ear no previous therapies; area 36 cm^2; thickness 2 mm according to multiple biopsies. **a** Day 0 before treatment, **b** application of ^{188}Re resin (Rhenium-SCT® in whole surface of the lesion + 3-mm safe margins; administered dose 856 MBq; dose received from the surface 127 Gy; mean dose 35 Gy; dose received from the deepest point of lesion invasion (2 mm) 14 Gy; treatment time 130 min. **c** Day 14 toxicity grade 3 according to the CTCAE scale [11]. **d** and **e** The lesion after 30 days, **f** after 48 days, **g** after 90 days, **h** after 12 months. Dermoscopy was negative, and no biopsy was performed. The patient has been classified as complete responder. Excellent cosmetic results according to RTOG scoring criteria [12]

observed cases; however, this could be related to different thickness of the epidermis in the legs as opposed to the face or trunk. Another possible explanation may be the different vascularization of the skin, making it faster for a wound to recover in the face than in the extremities.

With regard to skin toxicity, G3 toxicity in our population was rare (6.6%), and it would premature to draw any reliable conclusions. No direct and linear correlation between the absorbed target doses and the onset of G3 skin toxicity was observed. The only two factors who presented a statistical significance in our analysis were the mean absorbed dose (which is closely correlated to the volume of lesions) and the treated surface area, while the target and the superficial absorbed doses did not show any significance at the uni- multivariate analysis. There could be other important factors, which may play a role in the onset of G3 toxicity: in example different radio-sensitivity and repair capacity between different patients, different epidermal thickness in different anatomical districts or different general health conditions. The current study reports a preliminary experience of a single center. More data is needed to better understand the optimal dose to administer able to achieve a complete response with one single

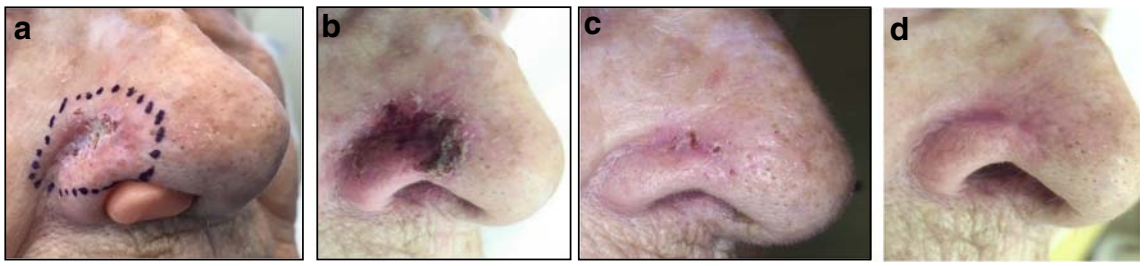

Fig. 3 Female 92 years old with relapse of a BCC of the right wing of the nose; previously treated with Mohs surgery; area 3.3 cm^2; thickness 0.4 mm according to multiple biopsies. **a** Day 0 before application of ^{188}Re resin (Rhenium-SCT®; administered dose 330 MBq, dose received from the surface 96 Gy; mean dose 52 Gy; dose received from the deepest point of lesion invasion (0.4 mm) 36 Gy; treatment time 23 min, **b** day 14 toxicity grade 2 according to CTCAE scale [11], **c** day 28, **d** day 60; **e** after 6 months, dermoscopy and biopsy were negative. The patient was classified as complete responder. Excellent cosmetic results according to RTOG scoring criteria [12]

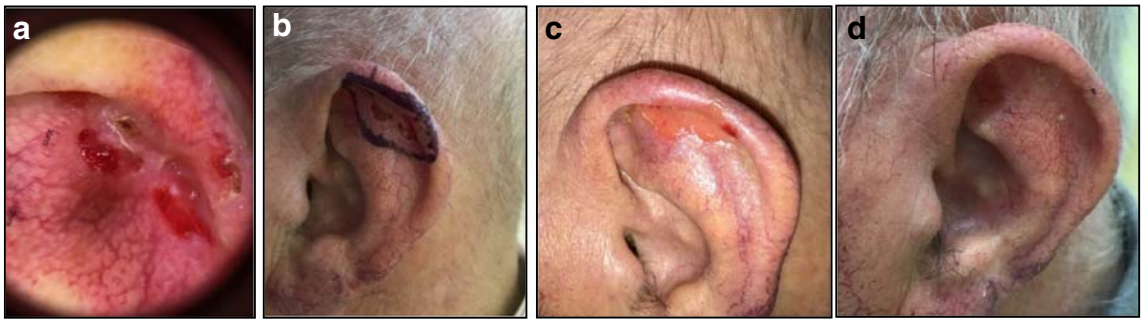

Fig. 4 Male 87 years old with relapse of a ulcerated BCC of the left ear previously treated with cryotherapy; area 3.0 cm^2; thickness 1.5 mm according to multiple biopsies. **a** Dermoscopy before the treatment, **b** day 0 before application of ^{188}Re resin (Rhenium-SCT®); administered dose 213 MB; dose; received from the surface 265 Gy; mean dose 84 Gy; dose received from the deepest point of lesion invasion (1.5 mm) 38 Gy; treatment time 83 min, **c** day 14 early toxicity grade 2 according to the CTCAE scale [11], **d** day 28 complete resolution of the wound, **e** after 6 months, dermoscopy and biopsy were negative. The patient was classified as complete responder. Excellent cosmetic results according to RTOG scoring criteria [12]

application without significant early side effects. According to our preliminary observations, in our future trials, the personalized dose to deliver should mainly take into account the location, the surface area and mean absorbed dose and/or the volume of the lesions.

In conclusion, Rhenium-SCT® is a single-session painless technique, tailored on the patients and well-tolerated, that can probably provide better esthetic results compared to surgery and good efficacy. According to our preliminary experience, the main advantages of this technique are (1) the possibility to apply the treatment to lesions with complex geometry or where the surface is not planar (ears or wing nose for example) where other noninvasive techniques such as high dose rate brachytherapy or external beam RT may have some difficulties in delivering an homogeneous high dose rate to the whole lesion. (2) The suitability of this treatment for even large lesions (up to 36 cm^2 in our population), where other treatment modalities may have some difficulties. (3) The possibility to use this technique in patients for whom surgical approach could be technically difficult or may result in a very poor outcome both from a functional or esthetic point of view. This is particularly true in patients in whom the lesions are located in the face, scalp, or ears.

A cost/benefit analysis of this treatment in comparison with other approaches is not in the aim of this preliminary study, however we would like to underline that Rhenium-SCT® can

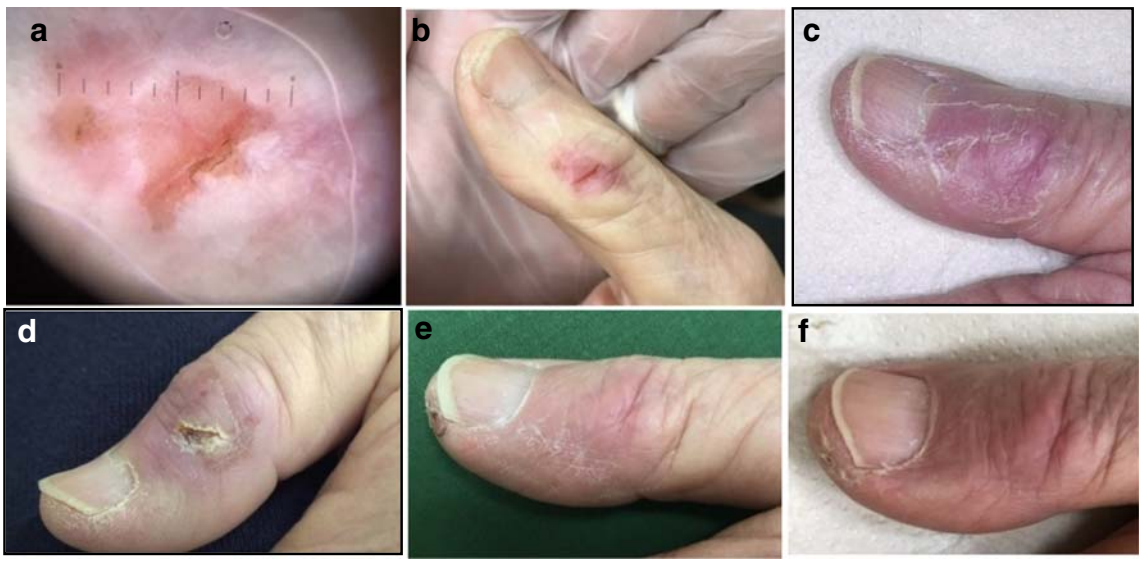

Fig. 5 Male 84 years old relapse of SCC of the first finger of the right hand previously treated with cryotherapy and C02 laser; surface 2.5 cm^2; thickness 0.6 mm according to multiple biopsies**. a** Dermoscopy before the treatment **b** day 0 before application of ^{188}Re resin (Rhenium-SCT®); administered dose 300 MBq; dose received from the surface 125 Gy; mean dose 58 Gy; dose received from the deepest point of lesion invasion (0.6 mm) 37 Gy; treatment time 25 min, **d** day 14 toxicity grade 1 according to the CTCAE scale [11], **e** day 28, **f** day 60, **g** day 90 after 6 months, dermoscopy negative and biopsy was not performed. The patient was classified as complete responder. Excellent cosmetic results according to RTOG scoring criteria [12]

be carried out on an outpatient day service facility and involves a relatively limited number of staff before, during and after the treatment. The average duration of a single application is only 76 min and many patients (from three to six in our experience) can be treated at the same time.

Main limitations

Despite this encouraging initial data, longer follow-up is needed in order to compare this treatment with its alternative competitors (brachytherapy or EBRT) by evaluating their long-term recurrence rate and, eventually, late side effects. A longer observation period is also needed to rule out the theoretical possible radio-induced local skin second malignancy.

A technical limitation is that the calculated absorbed doses (mainly mean and target) depend on the geometry of the tumors, which is frequently irregular. So, the exact volume of the lesions or the exact depth of neoplastic infiltration is difficult to calculate with high precision even according to multiple biopsies as we have performed in many cases. Accordingly, the data reported regarding the absorbed doses have to be taken with caution.

Conclusions

High dose brachytherapy using a nonsealed ^{188}Re resin (Rhenium-SCT®) is a noninvasive, easy to perform, and tolerable approach to treat NMSCs, and it seems to be an alternative when surgery or others. Radiation therapy techniques are not possible, not recommended or refused by the patient. Our preliminary results are very encouraging, since in our population ^{188}Re resin (Rhenium-SCT®) has shown to be effective in 98% of the treated patients. In the next future trials, larger populations and longer follow-up periods are needed to confirm these preliminary data and to find the optimal personalized dose in order to reduce early side effects.

Acknowledgments The authors want to thank Mar Olmeda and Joshua James Morigi for their precious contribution in the realization of this work.

Authors' contributions PC, FS, AF, and GML provided contribution to patient's data acquisition. LS, CP, FZ, SV, AGM, and PC provided substantial contribution to data analysis and interpretation. PC, FS, and GML drafted the first version of the manuscript. AGM and SF critically revised the first draft for important intellectual content. PC, CB, AP, AGM, and SF revised the manuscript for linguistic content. All authors approved the final version to be published.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Local Ethical Committee (23/2019/Oss/AOUBo).

Consent to participate Patients have signed written informed consent to participate.

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Personalized High-Dose-Rate Brachytherapy with Non-Sealed Rhenium-188 in Non-Melanoma Skin Cancer

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Abstract: *Objectives:* Most non-melanoma skin tumors are treated with conventional methods, being the most common surgery. However, satisfactory surgical treatment can be very challenging for patients with large or multiple lesions. In cases where the tumor is located on the face, hands or genital areas, the results may be suboptimal in terms of aesthetics and/or function. A high dose-rate brachytherapy using non-sealed Rhenium-188 was developed to offer a personalized solution for these cases as well as cases where a surgical approach was not preferred. Here we show a retrospective analysis of 43 patients treated with this technique.

Methods: The technique, called dermatological high-dose-rate beta-brachytherapy (DBBR), is a brachytherapy based on a non-sealed beta-emitter embedded in a complex specially-designed acrylic matrix. We use Rhenium-188 as the beta-emitter. This matrix is applied over the tumor, which is protected by a special thin plastic foil avoiding any direct physical contact of the radioisotope with the skin. After the calculated required amount of time, the protective foil with the applied radioactive acrylic matrix is removed. 43 patients (basal/squamous cell carcinomas, BCCs and SCCs) were treated with this technique after histological confirmation of the non-melanoma skin tumor. Patients were then followed up, to evaluate wound healing as well as potential side-effects and recurrences.

Results: 29 BCC and 14 SCC patients were treated with DBBR. 36/42 achieved complete clinical remission with only 1 application (24 BCC, 12 SCC) and 6/42 with 2 applications (4 BCC, 2 SCC); 1 BCC patient was lost to follow-up before wound closing. In 4 of the 6 patients (3 BCC, 1 SCC) treated twice the second treatment was planned due to the thickness of the tumor; in the remaining 2 patients (1 BCC, 1 SCC) the second treatment was needed to treat a recurrence at the border of the previously treated area. No side effects were reported. Wound healing was complete in 34-180 days (average 65 days, median 53) for all 42 patients that were followed-up. An average follow-up of 288 days (after one or two treatments) showed no single recurrence (42 patients).

Conclusions: DBBR is a very promising alternative for treatment of BCCs and SCCs for all cases in which a surgical approach is not recommended or accepted by the patient.

Keywords: NMSC (Non-melanoma skin cancer), BCC (Basal cell carcinoma), SCC (Squamous cell carcinoma), Brachytherapy, Rhenium-188.

INTRODUCTION

Brachytherapy has been used to treat skin tumors since the early 1900s [1]. As an alternative to electron beam device which have a large footprint and deposit a significant dose beyond the dermis due to secondary radiation, skin brachytherapy resulted to be a great option [2]. Among others, Iridium-192 is the isotope mostly used due to its long half-life (73.8 days) and its emission profile that includes beta (539-675 keV) and gamma radiation (296-612 keV). This combination made it possible to obtain high-doses in the epidermis without damaging underlying layers. Depending on the radioactivity and the isotope used, brachytherapy with sealed sources is classified as low (0.4-2 Gy/h), medium (2-12 Gy/h) or high-dose-rate (>12 Gy/h), the high-dose-rate being the most commonly used [3].

Iridium-192, Radium-226, Cesium-131, Iodine-125, Paladium-103 or other brachytherapy sources are sealed and commonly placed on the tip of a wire which can be introduced in so-called applicators. An applicator is usually bell-shaped and made of lead or tungsten. During the treatment, this applicator is placed over the skin tumor and the radioactive wire is introduced through a small aperture, such that it can irradiate the skin from a few millimeters distance during a controlled time, while the patient and the medical personnel are not exposed. Applicators can have different sizes, such that different tumor areas can be treated [4].

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E-ISSN: 2408-9788/17

This however poses a practical problem as tumors rarely are planar or have a regular shape. If the lesion to be treated is located in areas with complex geometry such as ears, lips or genitals, the placement of the applicator is cumbersome and dosimetry calculations can become very complicated. They are commonly oversimplified in the planning software [5].

In 2005, Sedda *et al.* proposed the use of a non-sealed radioactive matrix which could be applied over the tumor [6]. The idea was to bring the radionuclide as close to the tumor as possible, being independent of its three-dimensional shape. Sedda *et al* also introduced Rhenium-188 as the isotope which brought further advantages: Rhenium-188 emits stronger beta radiation (1.9-2.1 MeV) than Iridium-192, while its gamma component is in the range of gamma imaging (150 keV). As a result the dose distribution in the skin is less steep than for Iridium-192, but also drops to almost zero within the first millimeters [7].

These non-invasive approaches present significant benefits for non-melanoma skin cancer patients where the conventional surgical approach can be problematic or simply is not desired. This is the case of elderly people, where co-morbidities make surgery cumber-some or even contraindicated because it could result in negative side effects [8]. Also patients with large or multiple lesions are candidates for alternative therapies, since surgery could result in complicated interventions with multiple steps and sometimes including skin transplantation [9]. Finally with increasing patient awareness, patients with lesions on the face, the hands or the genitals may opt for non-surgical treatments in the hope of reducing the likelihood of unsatisfying aesthetic results or the loss of function [10].

MATERIALS AND METHODS

Our method for high-dose-rate brachytherapy prefers Rhenium-188 due to the following arguments.

a) Beta-emissions: With an energy spectrum in the range of 1.9-2.1 MeV, Rhenium-188's beta particles penetrate human tissue up to 1cm. However, 92% of the doses are deposited within the first 3 mm. Compared to Iridium-192, the dose distribution is less steep and has a lighter tail (Figure **1**).

b) Gamma-emissions: The main gamma component (15% of emissions) has energy of 150keV. This does not contribute significantly to the therapeutic aspect nor to the radiation burden to the patient and the users. Its presence makes it however easier to detect contamination, using conventional gamma detectors. Since 150 keV gamma photons can be detectedby conventional SPECT cameras, the latter could be used for therapy monitoring. This advantage plays a major role when comparing Rhenium-188 with Yttrium-90, which has a similar beta-emission profile (2.3 MeV) but no significant gamma nor X-ray component.

c) Half-life: If the irradiation is meant to be personalized and a non-sealed source is used, the half-life should be selected to be short to minimize the risk of incorporation and simplify logistics. This is different than in brachytherapy that is not personalized and uses sealed sources that should rather live long to minimize costs. With 17.0 h, Rhenium-188 is an excellent choice if compared to Yttrium-90 with 64.0 hours. As an example the amount of Rhenium-188 needed for treating an average patient can be disposed within 2-3 weeks, while the similar amount of Yttrium-90 would need 8-9 weeks.

d) Production: If personalized treatment is needed, the isotopes should be flexibly obtained. Rhenium-188 is commonly obtained from W-188/Re-188 generators. Likewise Y-90 can be obtained from Sr-90/Y-90 generators. In such a setup the decision in favor of Rhenium-188 is taken based on considerations about potential break-through of the mother isotopes and the impact of a potential incorporation as well as waste management. As it is well known from the data arising from the Techa river cohort, Stronium-90 is incorporated in the bones and has impact on the health of contaminated persons down to their offspring [11, 12]. With a half-life of 28.8 years Strontium-90 poses a bigger risk than Tungsten-188 with a half-life of only 69.4 days. Furthermore, Tungsten-188 is expected to have a major uptake only in the thyroid and a rather fast wash-out, as seen in experiments with mice [13]. On the side of waste management, a potential break-through of 1ppm would require storage of 272 days for Tungsten-188, but 112.6 years for Strontium-90.

In the initial work of Sedda *et al*, the radioactive material was applied directly over the tumor with only a thin layer of transparent petroleum jelly cream. This

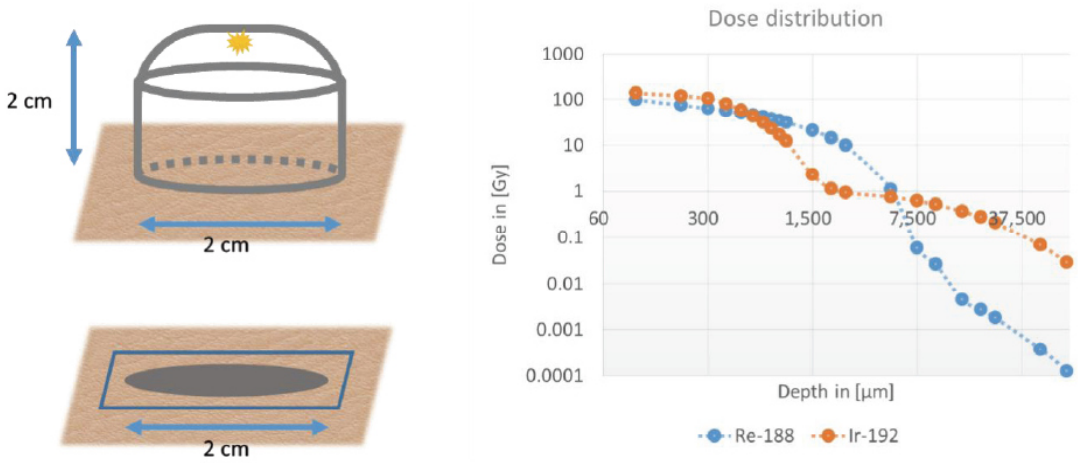


Figure 1: Right, dose at different skin depth for Rhenium-188 versus Iridium-192 for a comparable total dose of 65 Gy within the first 1.5mm. Simulations were performed using NRC's VARSKIN 5.2 software [14]. Left, schematics of simulated scenarios with VARSKIN.

layer was meant to minimize the risk of incorporation of the radioactive matrix through the skin or wounds. The highly insoluble dirhenium-heptasulfide was selected to avoid diffusion of the radionuclide through the matrix and later the jelly, but also its evaporation. Dirhenium-heptasulfide which forms microscopic particles (Figure **2**) can be obtained from perrhenate, the eluate of the W-188/Re-188 generators.

In order to further minimize the risk of incorporation, we introduced a sterile transparent surgical foil that covers the skin and makes it even harder for the radioactive particles to reach the skin. Several surgical foils were tested in terms of permeability as well as mechanical resistance to the dirhenium-heptasulfide and the components of the acrylic matrix. Additionally, the mechanical resistance of the foil was tested after irradiation with 100 Gy, which is above the planned use. "Aerofilm", manufactured by Aero Healthcare (UK), was selected as it fulfilled all pre-requisites and passed all tests.

The need for a sterile foil comes from the fact that sometimes skin tumors are ulcerated. Also, debulking the tumor may be useful by means of curettage or surgery in cases where it grew over the normal surface of the skin.

The next modification was to the application. A tool was designed to hold the radioactive matrix and apply it with a brush, while keeping it properly shielded with tungsten. In order to allow the operator to see the area being treated and at the same time protect his/her hand, a 10mm thick transparent PMMA glass was added to the tool. 10mm of PMMA essentially blocks the beta-emissions of Rhenium-188 completely (Figure **3**).

The complex specially-designed acrylic resin matrix and the Rhenium-188 in form of insoluble dirhenium-

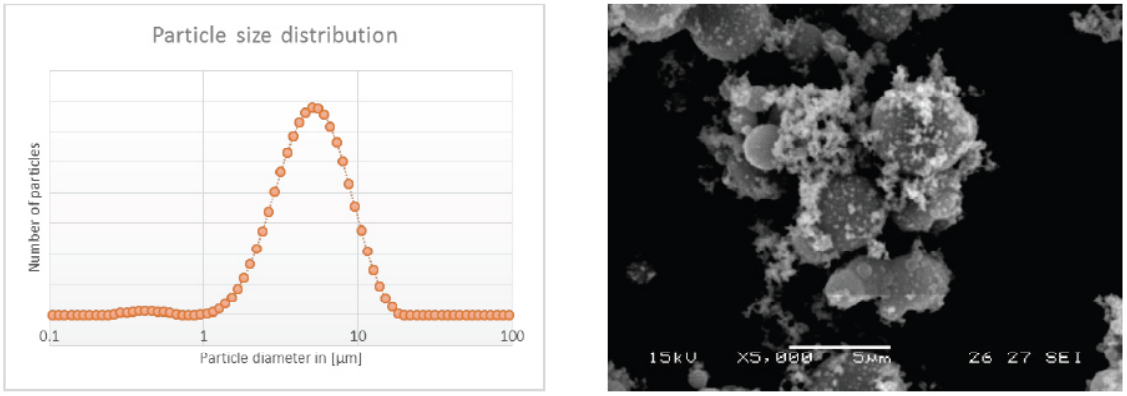
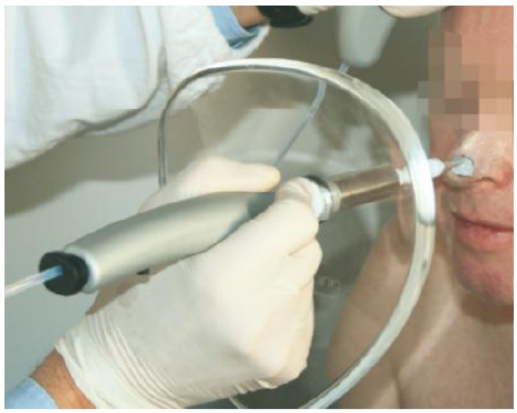


Figure 2: Left, particle size distribution of dirhenium-heptasulfide from our production. Right, scanning electron microscope image of dirhenium-heptasulfide particles (round).



Specific radioactivity per area (mCi/cm2)	Specific radioactivity per area (MBq/cm2)	0,5	0,75	1	1,5	2	2,5	3	4	5	7,5
0,38	14	268	254	247	237	234	230	227	225	222	219
0,41	15	248	235	229	220	217	213	210	209	206	203
0,43	16	231	219	214	205	202	199	196	195	192	189
0,46	17	216	205	200	192	189	187	184	183	180	177
0,49	18	203	193	188	181	178	176	173	172	169	167
0,51	19	192	182	178	171	168	166	163	162	160	158
0,54	20	182	173	168	162	159	157	155	154	152	149
0,57	21	173	164	160	153	151	149	147	146	144	142
0,59	22	164	156	152	146	144	142	140	139	137	135
0,62	23	157	149	145	139	138	136	134	133	131	129
0,65	24	150	143	139	133	132	130	128	127	125	123
0,68	25	144	137	133	128	126	124	123	122	120	118
0,70	26	138	131	128	123	121	119	118	117	115	113
0,73	27	132	126	123	118	116	115	113	112	111	109
0,76	28	128	121	118	114	112	110	109	108	107	105
0,78	29	123	117	114	109	108	107	105	104	103	101
0,81	30	119	113	110	106	104	103	101	101	99	98
0,84	31	115	109	106	102	101	99	98	97	96	95
0,86	32	111	106	103	99	98	96	95	94	93	92
0,89	33	107	102	100	96	94	93	92	91	90	89
0,92	34	104	99	97	93	92	90	89	88	87	86

Figure 3: Top left, tool for application of radioactive matrix on patient during a procedure. Bottom left, table used for calculation of treatment time for a given target depth (here a protocol of 50 Gy to 300 µm). Right, physician fully equipped with radiation protection clothes.

heptasulfide microparticles are contained in a single use sealed and calibrated “carpoule”, that is loaded into the application hand held tool.

For dosimetry calculations a set of tables was generated for different target depths (300, 400, 500, 600, 700 µm…) using the simulation software by the U.S. Nuclear Regulatory Commission (VARSKIN 5.2 [14]). The software was validated using measurements both in phantom setups and in patients [15]. Exemplary measured patient dose curves can be found in [6]. The overall concept is to determine the time needed for a (lethal) dose of 50 Gy to be delivered at a given depth. At the skin surface the dose rate is commonly >100 mSv/h. In terms of radiation dose for the rest of the body due to the gamma component, we calculated in the worst case scenario 0.85 mSv/GBq/h.

The result of the improvements is a simple 10 step procedure:

1. Delineation of the tumor border including a safety margin of 3-5 mm on the skin of the patient with a dermatological pen. The safety margin was selected to match the common margin used in surgery.
2. Determination of the area to be treated, in cm^2.
3. Covering of lesion(s) with the protective foil.
4. If treating area is near the eyes, covering of the eyes with lead protections. This step is of major importance to avoid damage of the eye lenses, in particular since up to 90% of all non-melanoma skin cancers are located on the face.
5. Loading of a carpoule into the application tool and measurement of the initial radioactivity.
6. Application of the radioactive ready-to-use matrix over the foil along marked area using the application tool.
7. Measurement of the remaining radioactivity in the carpoule in theapplication tool.
8. Calculation of treatment time based on the difference of initial and remaining radioactivity, the determined area to be treated and the target depth.

9. Removal of the foil with the radioactive matrix after the end of the treatment time.

10. Control of contamination.

Following the analysis of the database of the S. Eugenio Hospital, in Rome, we found 43 patients with 87 lesions who had a complete histological record, dosimetry information and imaging material suiting the evaluation in this work. The group consisted of 18 females and 25 males.

Lesions were located all over the body (Figure **4**). 4 patients had multiple lesions. All lesions were confirmed by histology. Where needed, epilumine-scence images where taken.

The method described above was used to treat the patients. If a scab was present it was removed before application of the foil. For this step the scab was first softened for several minutes with a saline solution. In case of multiple lesions, each lesion was treated separately.

For genitals and lips, a skin dose of 50 Gy was applied at 300 µm since mucous tissue is more sensitive to radiation; here the rationale is to do a fractioning in 2-3 treatments with 6-12 months between fractions. For relapses the irradiation depth of 50 Gy was set to 600 µm. For all other anatomies or situations the target dose was 50 Gy to 500 µm. BCC and SCC were treated equally.

Follow-up took place without a particular regime. In case a recurrence of the therapy was detected during follow-up a second treatment was considered.

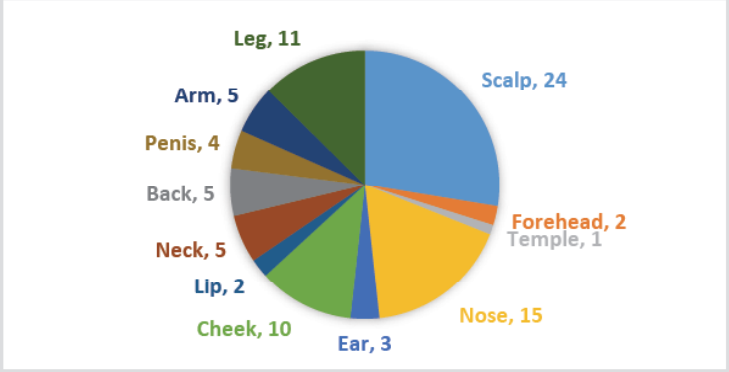


Figure 4: Distribution of lesion localization within the 43 patients.

Table 1: Distribution of Histology and Reason for DBBR given Anatomy. *Patient Lost to Follow-up had a Tumor on the Cheek. #Patient Lost to Follow-up was Treated due to Advanced Age

	Histology		Reason for DBBR			
	BCC	SCC	Age	Recurrence	Localization	Multiple
Scalp	24	0	1	0	0	23
Forehead	2	0	0	1	0	1
Temple	1	0	1	0	0	0
Nose	14	1	9	5	0	1
Ear	2	1	0	0	3	0
Cheek	7*	3	6#	3	0	1
Lip	1	1	0	0	2	0
Neck	5	0	0	0	0	5
Back	5	0	0	0	0	5
Penis	0	4	0	0	4	0
Arm	5	0	0	0	0	5
Hand	0	1	0	1	0	0
Leg	8	3	3	0	0	8

RESULTS

29 basal cell carcinoma (BCC) patients and 14 squamous cell carcinoma (SCC) patients were treated. One of the SCC patients had an in situ tumor (Bowen's disease). One of the BCC patients had a pigmented BCC, 4 of them were ulcerated, 1 was nodular and 1 was sclerodermiform. In all patients a surgery was not indicated due to anatomical localization (9), age (18), and multiple tumors (4) or as surgery had previously failed (11). Among the 11 patients that were unsuccessfully treated with surgery prior to therapy, 1 of them had one, 2 of them three interventions. Among the 4 patients that had multiple lesions, 1 of them had 23 lesions on the scalp, 1 had 20 lesions on arms, legs, neck, back and the forehead. Multiple lesions were treated in a single session regardless of the number of them.

Treatment times varied from 15 minutes to 2 hours, in average 61 minutes and median 59 minutes (Figure **5**). The dose-rate was in average 57.8 Gy/h (median 50.8 Gy/h). The treatment area varied between 1 cm^2 and 49 cm^2 (single lesion), in average the area treated was 5 cm^2 with a median of 3 cm^2 (Figure **5**). Application was painless in all cases. No single side-effect or adverse event was reported during treatment. Contamination was not found in any of the cases confirming the impermeability of the foil. In 2 cases due to a tumor thickness > 500µm or in 2 cases due to anatomical location (ear and penis), the treatment was planned to be performed in 2 steps with roughly 6 months interval.

3 to 4 days after treatment a radiation-induced wound appeared, however this disappeared completely within 30 to 154 days (average 65, median 53) depending on the area of the lesion, the body part and the age of the patient. Wound closing was fastest for small lesions of younger patients, while larger lesions of older patients took more time to close and the redness to disappear. After application if any bleeding was present before treatment stopped in a few days. Also some lesions produced a clear serum during the first 1-2 weeks, but it disappeared without needing any action. From an anatomical point of view, noses and cheeks healed the fastest while legs took the longest.

All 44 patients achieved complete remission of the skin. The average follow-up time was 288 days (35-1150 days, median 212 days). 34 patients had a follow-up of more than 3 months (116-1150 days, median 304 days). 24 patients had a follow-up of more than 6 months (210-1150 days, median 388 days). 1 patient (BCC, recurrent patient after 3 surgeries) was lost to follow-up. The 4 patients planned to get 2 treatments showed complete remission after the second treatment. 2 patients needed a second unplanned treatment for complete remission as the security margin showed to be too tight resulting in a recurrence at the border of the treated area. No relation between BCC and SCC and success / recurrence rates was observed in this group. No single side-effect was reported beyond the radiation wound during the first 30-154 days, in particular, no haematological toxicity was observed which confirms that no Rhenium-188 was incorporated. No medical intervention was needed to treat the local reaction as it healed on its own for all 44 patients in all treatments. No pain was present during the healing process.

DISCUSSION AND CONCLUSIONS

The treatment of skin cancer with radioisotopes has been performed since the 1960s. As an alternative to soft X-ray and electron beam irradiation, brachytherapy with sealed sources achieves local control rates of 90 to 100%. Like conventional radiotherapy, its application is recommended as second line treatment for patients

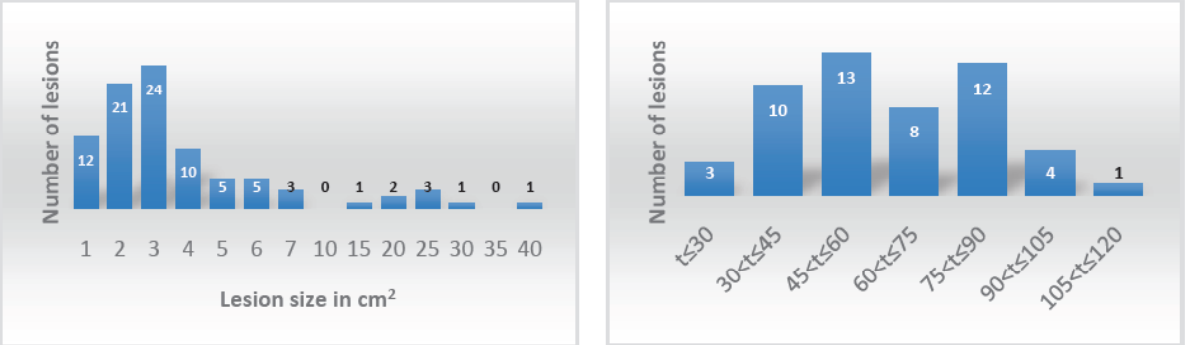


Figure 5: Left, histogram of lesion size for all 88 lesions. Right, histogram of treatment times for all 49 treatments (37 single treatments and 6 double treatments).

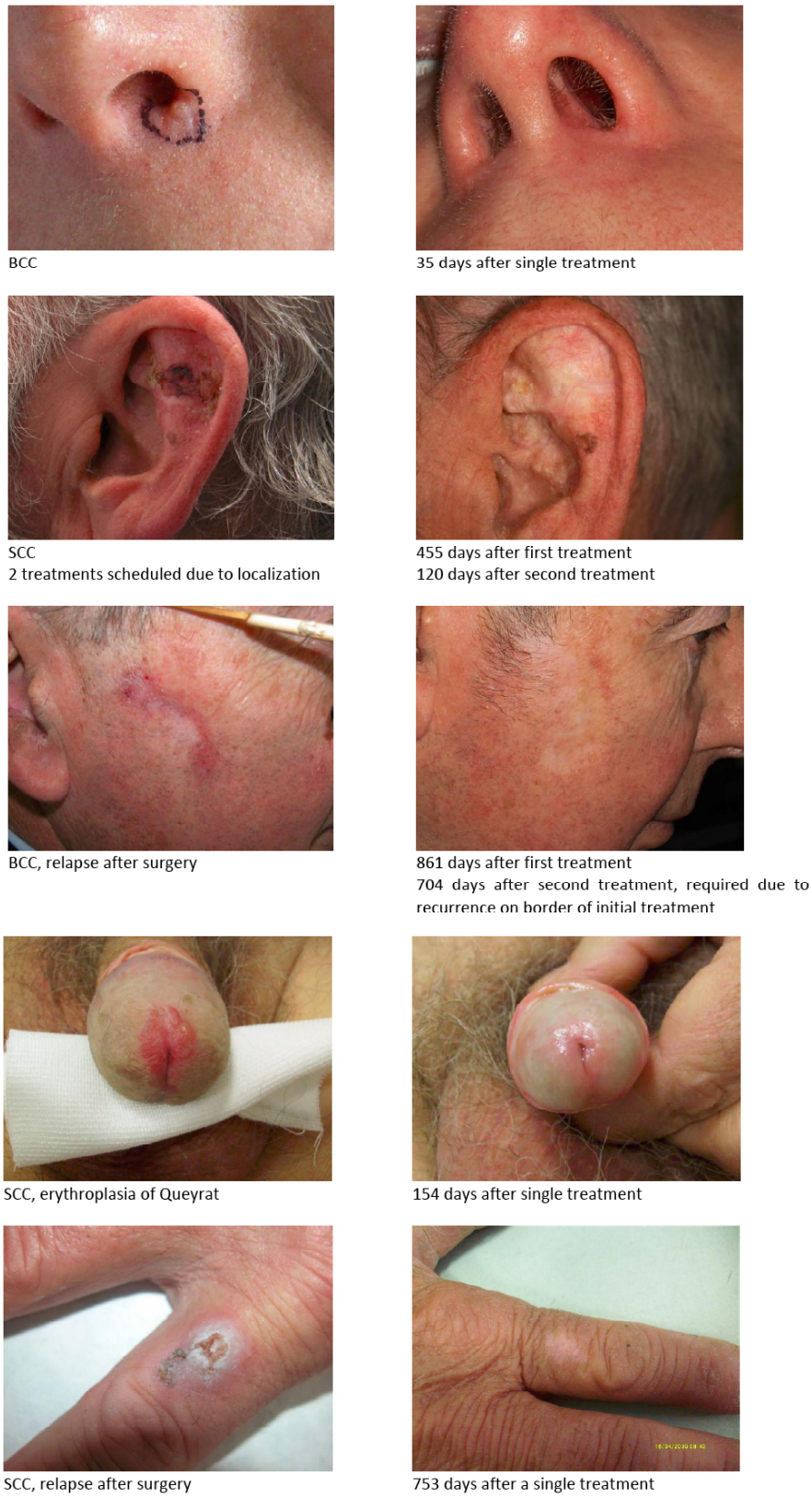


Figure 6: Examples of lesions treated before and after the brachytherapy with Rhenium-188.

with lesions where surgery cannot be applied or where a suboptimal result is expected [2].

While the use of high radioactivity Iridium-192 in sealed form has become the standard (HDR skin

brachytherapy), the approach of Sedda *et al.* using non-sealed Rhenium-188 brings advantages, in particular in terms of personalization.

1. Personalization: By binding the radionuclide to a liquid viscous matrix and applying it directly over the tumor, the exact shape of the lesion and a desired security margin can be covered. As a result, healthy tissue can be spared, and a complete conformational radiotherapy is performed. Furthermore the dosimetry is calculated on a lesion-by-lesion base and the treated depth can be easily controlled by varying the time the radionuclide stays over the tumor.

2. Dose distribution: Rhenium-188 has a flatter dose distribution in depth than Iridium-192 providing thus a more homogeneous dose to the tumor. On the other hand the rapid drop of dose after 3 mm spares underlying tissue layers. This is particularly of importance for mucous tissues like lips and genitals, but also for ears where it is of great importance to spare the cartilage, and for eye lids due to the radiation sensitive eye lenses.

3. Applicability: The radioactive cream can be applied independently of the 3D surface and the anatomical position of the tumor. This advantage creates therapy options for anatomies, such as inside the ear or in the genital area, where sealed source brachytherapy cannot be applied. Since the radionuclide is applied over the skin, there is no risk that the patient moves relatively to the source. This improves the comfort for the patient, avoids the irradiation of healthy tissue and reduces the risk of not reaching the target dose for the tumor.

4. Single-session: In contrast to conventional radiation therapy and brachytherapy with sealed sources, a single treatment is sufficient in most cases with the proposed method. A second or third treatments are planned only for cases with thick tumors or in mucous tissues. In that case, these applications are separated by 5-7 months. Such a treatment plan simplifies the logistics and the patient comfort, as most patients are elder people who benefit from not having to come for fractions many times a week during several weeks. Furthermore, there are no repositioning issues.

On top of the above-mentioned advantages, the ones of conventional radiation therapy also apply. DBBR is painless, fast (in average 60 minutes) and leaves in most cases no scar (in some cases a faint discoloration of the skin is present, which can slowly disappear, as seen in conventional radiation therapy). As there is no need of anesthesia it is an ideal approach for elder patients.

The current retrospective analysis shows good treatment results with no reported side effects. With a 100% remission rate after two treatments and the need of an unplanned second treatment in only 2 cases, this patient group confirms the reports of Sedda *et al.* [6, 7] and the expectations from the therapy. Tumors on susceptible areas like ears, lips and genitals are recommended to be treated in several steps. The same applies to thick tumors or recurrent lesions in particular on the nose. Care needs to be taken to define sufficiently wide margins to avoid a second treatment. On the whole, DBBR is a safe alternative therapy for BCC and SCC practically independent of tumor shape and anatomy which shows good potential to become a valuable tool for cases where surgery cannot provide a satisfying solution.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Anna-Maria Carrozzo, Dr. Jiyeon Kim and the teams of MAVIG GmbH, GBN Systems GmbH and OncoBeta GmbH.

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Dermo beta brachytherapy with ^{188}Re in extramammary Paget's disease

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***Aim*. Extramammary Paget's disease (EMPD) is a rare neoplastic pathology involving the vulva, scrotum, and perianal areas, and it is characterized by a slow and insidious course. EMPD may also be associated with internal malignancy, and its clinical presentation features long-standing pruritic lesions, eczema-like, refractory to any therapy. The pathogenesis is unclear, and univocal standardization of treatment is yet to be determined. As regard to the patients who suffer from it, women are more often affected than men. The therapeutic approach depends on the extent of involvement; wide surgical excision is the first choice among treatments, but other forms of therapy, alone or in combination, include imiquimod 5%, photodynamic therapy, Mohs surgery as well as external beam radiotherapy and Brachytherapy. In the present paper a new therapeutic alternative is proposed: Dermo-Beta-Brachytherapy (DBBT) with ^{188}Re.**

***Methods*. Five patients with EMPD, one secondary and four primary cases, have been treated by Brachytherapy with DBBT. This therapy has been successfully used for non-melanocytic skin tumors and basically consists in the topical application of a specially designed, tailor-made mould containing a radioactive beta-emitting isotope, rhenium-188.**

***Results*. The patients healed completely, after one session in one case and after two sessions in four cases, with 34 months mean follow-up.**

***Conclusion*. Brachyterapy could represent a new alternative therapy, instead than invasive treatments as surgery and conventional radiotherapy, capable to treat EMPD independently of its extension, with aesthetic and functional satisfactory results.**

KEY WORDS: Paget disease, extramammary - Brachytherapy - Adenocarcinoma.

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Extramammary Paget's disease (EMPD) is a cutaneous adenocarcinoma, with intraepithelial infiltration of neoplastic cells, showing glandular differentiation. It mainly affects the anogenital region and it manifests particularly in elderly patients, most of whom are women. EMPD can be primary, with no association with internal malignancies, or secondary, when it is associated with regional neoplasm (urogenital or intestinal). Primary EMPD has been hypothesized to derive either from the intraepidermal cells of the apocrine gland ducts, as supported by the presence of Folliculo-Sebaceous-Apocrine Units in anogenital and axillary regions, or from pluripotent keratinocyte stem cells.[1] The early symptom is pruritus, with the appearance of erythematous-eczematous lesions in the anogenital region, resistant to any topical therapy with steroidal and antibiotic creams. In addition to the treatment of urogenital cancer, if present, different therapies have been used in EMPD: the first choice is surgical excision, although other types of therapy are currently used, in particular imiquimod,[2, 3] photodynamic therapy [4] and 5-fluorouracil.[4] Radiotherapy has been employed, with good results, and different methods can be used, from external X-ray or electron beam irradiation to classical gamma emitter brachytherapy.[5] Brachytherapy in Paget's disease has been

successufully used in only one perineal case;[6] in this paper the authors have used a custom made wax cast with several catheters emitting X-radiation, confirming the better capacity of brachytherapy to adapt to body contour in this particular region.

In the present paper, a new type of brachytherapy, defined here Dermo-Beta-Brachytherapy (DBBT) is proposed for treating EMPD. It is based on the use of individually tailor-made radioactive mould sources with High-Dose-Rate (HDR) beta radiation. In this technique, a synthetic inert matrix containing a radioactive beta-emitting isotope is applied on the surface of the tumor lesion, so that only the tumour lesion is subjected to brachytherapy irradiation.[7]

Materials and methods

To prepare the irradiation sources, a certified ready-to-use kit has been used (Re-SCT ™, ITM, Munich, Germany). It basically consists of a synthetic complex matrix, in which a nanocolloid containing ^{188}Re beta emitting isotope is evenly distributed. The isotope ^{188}Re is a mixed beta – gamma emitter, with a half-life of 16.98 hours and ß-particles with a maximum energy of 2.12 MeV. The skin area to be treated was outlined by a dermographic pen, using accurate visual examination and dermoscopy. The skin lesion was then protected by the thin layer of a flexible, specially designed, adhesive plastic foil, to prevent any direct contact of the radioactive material with the epidermis. The radioactive source was applied on the tumor lesion, above the protective plastic layer, using a specially designed shielded ergonomic applicator, which contains the carpoule with the radioactive matrix. After several minutes, the matrix solidified, without shrinkage; the radioactive mould was kept on the lesion for the time sufficient to release the precalculated dose. The administered dose depends on the initial radioactivity, the isotope emission energy, the area of the lesion and the contact time. Due to the use of radioactive material, brachytherapy treatments were in all cases performed inside a Nuclear Medicine Department, under the supervision of a dermatologist.

The irradiation area included both the evident lesion and the apparently healthy tissue border of 2-4 mm beyond the lesion. For each patient and each lesion, the irradiation area was measured, and the dose distribution curve was calculated, using a multi-point source, real-time integration software program (Varskin 3). At the end of the irradiation time, which ranged from 30 to 60 minutes, the radioactive mould was easily removed using a specially designed remote tong device, and it was discarded as radioactive waste.

Immediately after treatment, a faint redness of the treated area was clearly visible. After a few days, a variable erythema was present, in some cases with emission of serum, followed by scab formation. Over a period of 3-4 months, apparent clinical healing occurred.

Clinical cases

The five patients treated with EMPD are described below, and have been summarized in Table I.

Patient 1, a 67-year-old man, came to our attention for an erythematous area on the surface of the glands around the urethral orifice (Figure 1). A punch-biopsy showed pagetoid cells in the inferior part of epidermis, strongly positive for Cytokeratin-7; based on this, the man was diagnosed with EMPD. The patient reported that he had undergone surgi-

TABLE I.—*Clinical series.*

Number of patients (sex/age) - Localization	Diagnosis	Date first session (dose for depth)	Date second session - Site of relapse (dose for depth)	Follow-up (months)
1- (M/67 yrs) Glans	Secondary EMPD	III.2008 (50 Gy for 300 µ)	VII.2009-center (50 Gy for 300 µ)	Died for disease (28 months)
2- (F/65 yrs) Perineal/vulvar	Primary EMPD	I.2009 (50 Gy for 300 µ)	XII.2009-periphery (50 Gy for 300 µ)	AWD (48 months)
3- (F/59 yrs) Vulvar	Primary EMPD	XII.2009 (50 Gy for 300 µ)	IV.2012-periphery (50 Gy for 300 µ)	AWD (37 months)
4- (F/74 yrs) Perivulvar	Primary EMPD	IV.2010 (50 Gy for 300 µ)	No	AWD (33 months)
5- (F/79 yrs) Perivulvar	Primary EMPD	XI.2010 (50 Gy for 300 µ)	IX.2012-center (50 Gy for 300 µ)	AWD (27 months)

AWD: alive without disease.

cal excision of a bladder tumour 6 years earlier. A brachytherapy session was performed (Figure 2), and an apparent remission was achieved three months after treatment. After further 16 months a second session of DBBT was performed due to the presence of some erythematous areas; after this session a clinical total remission was achieved (Figure 3). One year after the last brachytherapy, the primary bladder tumour spread out and the man died of metastatic cancer (follow-up: 28 months). Before the death no clinical sign of relapse of EMPD had been observed.

Patient 2, a 65-year-old woman, presented an itchy erythematous lesion in the perineal and vulvar region for as long as one year, this lesion had not responded to various types of topical therapy (Figure 4). A biopsy was performed, EMPD was diagnosed. The lesion was cytokeratin-7-positive and cytokeratin-20-negative, confirming that the woman had primary EMPD (Figures 5, 6). Based on radiologic and ultrasound examinations, we excluded involvement of the urogenital apparatus. The woman underwent two treatments of brachytherapy (DBBT), the second session eleven months after the first one. The last session was performed because of the appearance of the disease outside the area treated the first time, resulting in the clinical healing of the lesion (Figure 7). A histological examination performed three months after the second session showed that the neoplastic cells had disappeared (Figure 8). A 48-months follow-up confirmed the complete remission of the disease.

Patient 3, a 59-year-old woman, presented an itchy dermatosis in the vulvar region, which was resistant to common topical therapy. In the inferior perivulvar region, an erythematous-eczematoid lesion was also present. A biopsy was performed, and EMPD disease was diagnosed, with cytokeratin-7-positive and cytokeratin-20-negative. Based on clinical and CT/Ultrasound, urogenital neoplastic disease was excluded, confirming that the woman had primary EMPD. A brachytherapy session was then performed, with apparent clinical healing of the lesion. Four months after therapy a histological examination confirmed the disappearance of the neoplastic cells. After 29 months, on the left border of the treated area, a small tumor area was observed, and a second session was performed with the complete healing of the lesion. A 37-months follow-up confirmed the complete remission of the disease.

Patient 4, a 74 year-old woman, presented an itchy dermatosis in the perivulvar region, with onset one year earlier. Her condition had not responded to topical steroid therapy. Histological examination was performed, and EMPD was diagnosed; the lesion was cytokeratin-7-positive and cytokeratin-20-negative, confirming that the woman had primary EMPD. Involvement of the urogenital apparatus was excluded based on radiologic and ultrasound examinations. A brachytherapy session was performed on the mucosa of the left major labium and of vaginal ostium, with apparent clinical healing of the lesion. Histological examination after three months showed that the neoplastic cells had disappeared. A 33-months follow-up confirmed the complete remission of the disease.

Patient 5, a 79 year-old woman, was examined for suspect vulvar localization of psoriasis. She presented an itchy dermatosis in the perivulvar region, with onset two years earlier; the dermatosis had not responded to specific antipsoriasis topical therapy. Histological examination was performed and EMPD was diagnosed; the lesion was cytokeratin-7-positive and cytokeratin-20-negative, confirming that the woman had primary EMPD. Involvement of the urogenital apparatus was excluded based on radiologic and ultrasound examinations. A brachytherapy session was performed, with clinical recovery of the lesion, and histological examination four months after therapy confirmed the disappearance of the neoplastic cells. Twenty months later a small erythematous area in the right major labium appeared, and a second session of DBBT was performed with complete remission of the disease. Follow-up after 27 months confirmed the complete healing.

Results

The results for the 5 patients were as follows: all the patients showed complete remission of the disease without histological evidence of tumor at the end of the treatments. One patient (N. 4) was submitted to one session and four patients (N. 1, 2, 3, 5) were submitted to two sessions. Among these last four patients, two (N. 1, 5) had presented relapse inside the treated area, probably due to an insufficient dose delivery in the tumor area, the other two (N. 2, 3) had presented relapse at the periphery of the previously treated areas, probably due to the irregular peripheral extension of EMPD. The mean duration of follow-up was 34 months. In the days immediatly after the therapy, the side effects of this treatment consisted in burning sensation and superficial erosions, followed by small crusts, which resolved in two-three weeks after DBBT session. These side effects have been managed with a topical emollient cream, camomile compress and anti-septic washes. Sometimes analgesic drugs have been associated.

Discussion

The percentage of secondary EMPD, in respect to all cases of EMPD, is around 11-45%.[8] Primary and secondary EMPD cannot be differentially diagnosed with histological examination alone, and immunohistochemical analysis is necessary.[9] Some authors have proposed that GCDFP-15 reactivity can be used to distinguish between primary and secondary

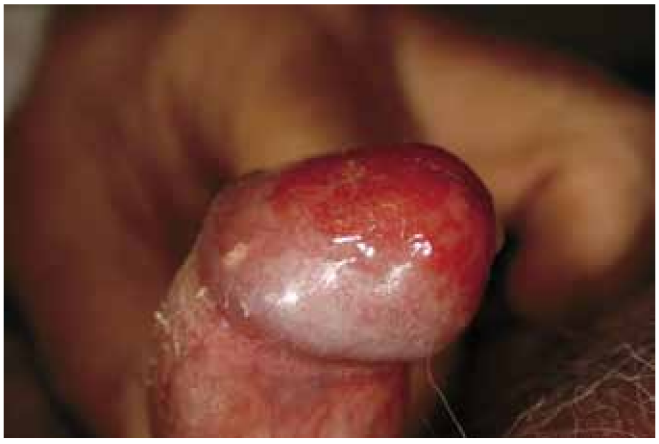

Figure 1.—Patient 1, gland with EMPD.

Figure 2.—Application of brachytherapy mould.

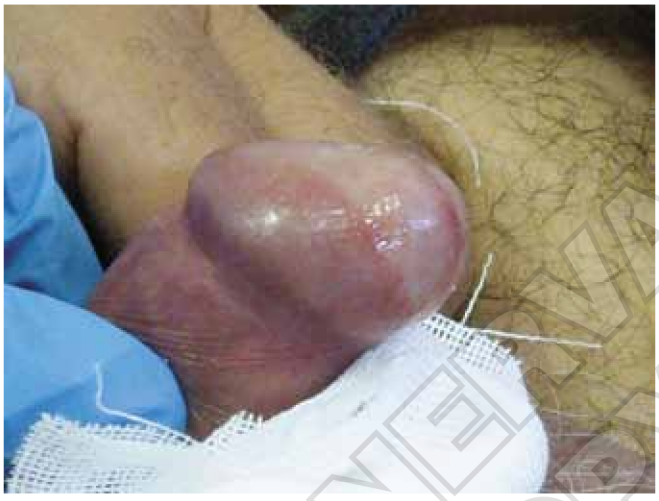

Figure 3.—Clinical healing of the lesion, after therapy.

Figure 4.—Patient 2, vulvar and perineal EMPD.

EMPD.[10] A complete clinical evaluation should always be performed, including a full cutaneous examination, a lymph node examination, a colonscopy and a cistoscopy. Furthermore, a thorough examination of the breast and pelvis should be performed in female patients, and an examination of the prostate and testes should be performed in male patients. To date, the most appropriate therapy for EMPD has been surgery, with the excision exceeding 1 cm of the normal skin margin. The rates of recurrence after surgery are high (15-43%),[5, 11] as EMPD can extend with finger-like projections from the main tumor body.[12]

Mohs surgery is considered an useful therapeutic strategy to ensure "safe" surgical margins. The use of intraoperative immunohistochemical methods with antibodies directed against cytokeratin-7 can improve the visualization of Paget's cells extending periferically from the tumor,[12] with an 8-28% reduction in local recurrences.[11-13]

Other therapies have been used in clinical practice. In particular, imiquimod, an immune modifying-agent, has been successfully used in intraepithelial EMPD, although the longest follow-up period reported in the literature for vulvar disease is 26 months. Imiquimod is applied daily for three weeks followed by an application on alternate days for other three weeks.[2] Some cases of EMPD have not responded to Imiquimod.[3]

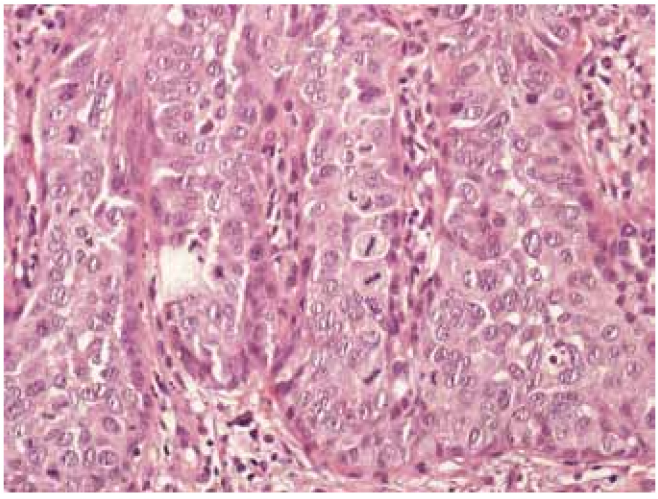

Figure 5.—Epidermis with proliferation of paget cells, atypia and mitosis.

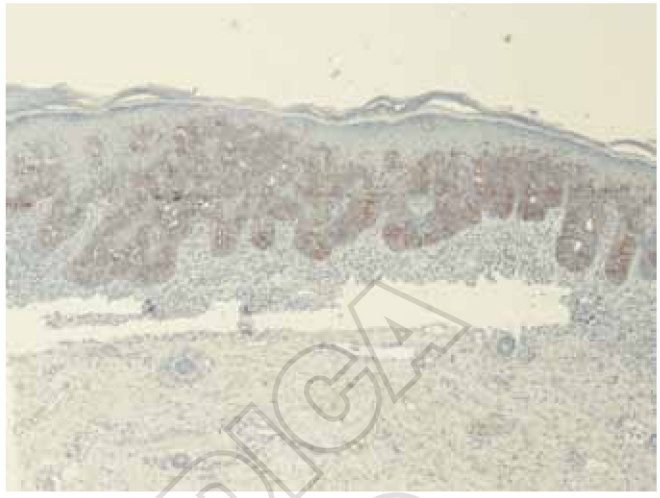

Figure 6.— Immunohistochemistry with CK 7, marking neoplastic cells.

Figure 7.—Clinical healing of the lesion, after therapy.

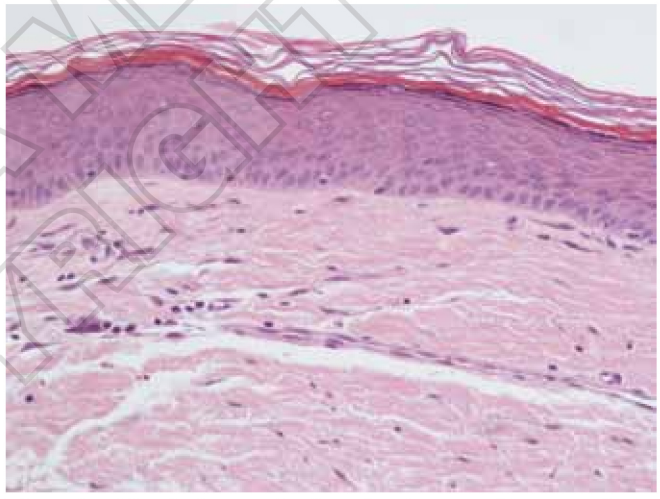

Figure 8.—Histologic examination after therapy, without neoplasia.

Photodynamic therapy with intravenously injected porfimer sodium, and irradiation with an argon-pumped dye laser with a continuous wavelength of 632 nm, have also been used. A complete response was achieved in 78% of the treated cases, who had a median follow-up of 62 months; the results were better than the ones achieved with classic topical aminolevulinic acid (ALA) photodynamic therapy.[4]

Classic radiotherapy (RT) can be used as a single therapy for initial disease, for focal recurrences after complete surgical excision, or as a postoperative adjuvant therapy. It can also be used in medically inoperable cases, or if the patient refuses surgery; a radiation dose of 60 Gy is required, however a high recurrence rate is present.[5]

Brachytherapy (BT) is a radio-therapeutic method in which the source of radiation is placed at a short distance (the term "brachy" is ancient Greek for "short"), above or into the target tissues (intracavity, transluminal, interstitial). BT is categorized as low dose rate (0.4-2 Gy/h), medium dose rate (2-12 Gy/h), or high dose rate (greater than 12 Gy/h). HDR-surface-mold BT has been used, in most cases with

gamma-emitting isotopes such as 192-Ir. The use of Beta emitter isotopes ^{188}Re [2] or ^{166}Ho [14] has been recently introduced into clinical practice.[15] BT with catheters has been used to treat recurrences of EMPD after surgery, with good results.[6]

Surface-mould BT with catheters delivering Iridium-192 has been used in recurrent non-melanoma skin cancer,[16] with large and irregular surface areas; the therapy has shown better cosmetic and functional results compared to those obtained with external beam RT.

All the radiotherapic treatments described above, because of their penetrating nature, can however cause damages in adjacent or underlying tissues. As regard to these side effects, the method proposed in the present paper represents a significant improvement. DBBT is a superficial, highly selective beta emitter radiotherapy, which has the advantage of being therapeutically effective only at short distances. Therefore the underlying healthy tissue is spared, as beta radiation deposits more than 90% of the dose in the first two mm of the skin, the maximum depth usually involved in tumor invasion. In the present work, the beta emitters were distributed (see the Materials and Methods section) in a matrix that is able to adapt to every skin surface, administering an accurate dose distribution on the entire lesion and sparing the healthy tissue.[7] A typical real-case dose absorption curve in human tissue for the beta emitter ^{188}Re is shown in Figure 9. The dose distribution curve (according to software Varskin 3), corresponding to the treatments performed in the present study, shows a clear decrease in dose, from a nominal value of around 60 Gy in the epidermis, to less than 15 Gy at a depth of only 1.5 mm, a depth value that can be considered a limit for the invasion in these tumors. The choice of the apparently healthy tissue to be included in the irradiation is an important parameter, since a lethal dose must be administered to the potentially infiltrating cells in the outer edge.

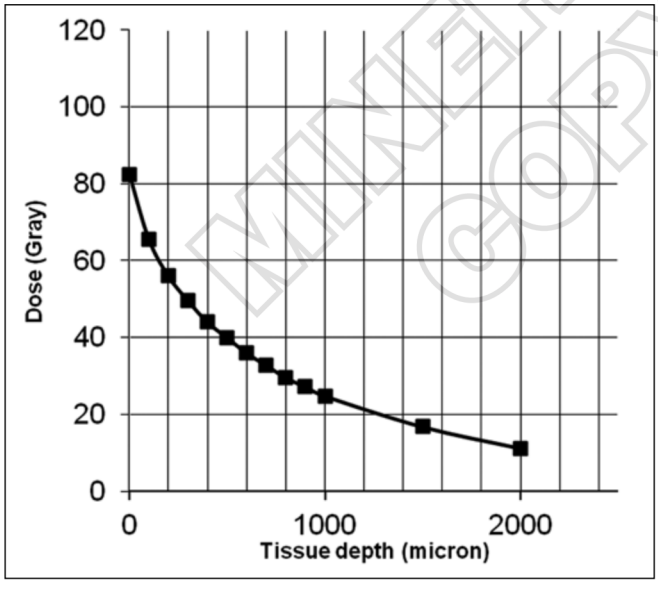

Figure 9.—Dose absorption curve in human tissue for the beta emitter ^{188}Re (according to software Varskin 3).

Conclusions

The present paper is the first report of a surface-mould beta emitter brachytherapy in EMPD, and the clinical results are quite promising. The four primary EMPD cases healed with a mean negative 34-months follow-up. The only secondary EMPD case (Patient 1), in spite of the local healing, died for metastatic bladder cancer.

This nuclear medicine technique could be an alternative therapy not only to medical treatment but also to surgery in EMPD selected cases. The technique is rapid and safe, and offers the possibility to perform a conformational radiotherapy, strictly following the real tumor edge, and without dose deposition in the subdermal tissue, independently of the shape complexity and number of lesions. The treatment is mostly performed in one or two therapeutic sessions, without discomfort for the patient. The need for a second treatment at the periphery of treated areas in two of our patients (N. 2, 3) is really not surprising, due to the particularity of EMPD, which tends to spread in highly irregular fashion and may have finger-like extensions, which grow beyond the primary tumour[12]. In these two patients the relapse was localized outside of the edge of the first area treatment and in both cases the second session was successful. On the other hand in the patients number 1 and 5 a new tumor appearance was localized inside the treated area; this fact could be explained by the non-uniform radiobiological action of the beta radiation and to the dishomogenous conformation of the neoplastic epidermis. Nevertheless, also in these patients, a second session was resolutive. A further explanation lies in the fact that a relatively low dose was administered to the lesions, due to the low thickness of epidermis and semimucosa in genital areas.

The protocol of the dose distribution curve for non melanocitic skin tumors (BCC and SCC) usually consists in a dose of 50 Gy for 500 μ; the dose administered to the patients of the present paper was 50 Gy for 300 μ. This choice was made considering the lesser depth of skin in the areas affected by Paget, in order to minimize the damage to underlying tissue of the patients. The application of a second session of DBBT, especially in central already treated areas, could probably increase the late radiation-induced side-effects, but the few treated cases and the short follow-up cannot assess these side-effects.

In spite of the low number of the treated cases, we think that the results are quite promising and DBBT could be a real alternative therapy for selected EMPD patients. Our patient's follow-up and new enrolled cases, will better confirm the validity of this new radiotherapic treatment.

Riassunto

Morbo di Paget extramammario: dermo beta brachiterapia con 188-Re

Obiettivo. Il morbo di Paget extramammario è una rara malattia neoplastica che colpisce generalmente la regione vulvo-perineale, perineo-scrotale e perianale, ed è caratterizzata da un decorso lento ma insidioso. Tale malattia può essere secondaria a una neoplasia viscerale (forma secondaria). Clinicamente si presenta con un quadro clinico simile a una dermatite eczematosa, pruriginosa e resistente alle terapie con incidenza maggiore nel sesso femminile. La patogenesi non è chiara e non esiste un protocollo terapeutico standardizzato. Le opzioni terapeutiche sono la chirurgia, la radioterapia/brachiterapia, la terapia fotodinamica e nuove terapie topiche (ad es. imiquimod). Nel presente articolo viene proposta una nuova terapia: la Dermo Beta Brachiterapia (DBBT) con ^{188}Re.

Metodi. Cinque pazienti affetti da morbo di Paget extramammario, un caso secondario e quattro primitivi, sono stati trattati con dermo beta brachiterapia con ^{188}Re, terapia già precedentemente utilizzata con successo nei tumori cutanei non-melanocitari. Tale terapia consiste nell'applicazione locale di una speciale resina sintetica contenente l'isotopo beta-emittente ^{188}Re, per un tempo limitato e poi viene rimossa.

Risultati. I cinque pazienti sono guariti completamente, in un caso dopo una singola sessione terapeutica e negli altri quattro casi è stato necessario effettuare una seconda applicazione. Il follow-up medio è stato di 34 mesi.

Conclusioni. La dermo beta brachiterapia con ^{188}Re può rappresentare una nuova alternativa terapeutica, in grado di risolvere il morbo di Paget extramammario, anche nelle forme più estese, sostituendo la terapia chirurgica e la radioterapia classica, trattamenti più invasivi e con maggiori effetti collaterali (cicatrici disfunzionali).

PAROLE CHIAVE: Morbo di Paget extramammario - Brachiterapia - Adenocarcinoma.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on July 9, 2013.

Accepted for publication on October 23, 2013.

Eur J Dermatol 2013; 23(2): 183-8

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Article accepted on 11/4/2012

Dermo beta brachytherapy with 188-Re in squamous cell carcinoma of the penis: a new therapy

Background: Squamous cell carcinoma of the penis (SCCP) is the most common penis neoplasia, favoured by phimosis, HPV infection and scleroatrophic lichen. The classic therapy is surgical with anatomic demolition, which often causes important psychological problems. Other non-demolitive therapies can be utilized, such as radiotherapy, brachytherapy and topical medical treatment. *Objectives:* we propose a new non-invasive therapy called "Dermo beta brachytherapy (DBBT) with 188-Re" in which a synthetic inert resin-matrix containing a radioactive beta-emitting isotope is applied on the surface of the tumor lesion. *Materials and methods:* a total of 15 patients with a histologically confirmed diagnosis of SCCP were enrolled for treatment (DBBT). *Results:* of the 15 patients, 12 healed, 1 was lost at follow-up and 2 did not respond to therapy. *Conclusion:* The results indicate that DBBT is an effective treatment for SCC of the penis, sparing the anatomical integrity of the organ, and allowing normal sexual activity.

Key words: squamous cell carcinoma of penis, brachytherapy, dermo-beta-brachytherapy, surface mould brachytherapy

doi:10.1684/ejd.2013.1927

Squamous cell carcinoma of the penis (SCCP) is a rare neoplastic disease which represents less than 1% of all cancers in men. In North America and Western Europe, the incidence of SCCP is around 1 per 100,000 population, whereas in Asia, Africa, and South America, the incidence reaches 10-20 per 100,000 population as a result of socioeconomic and cultural factors [1].

SCCP occurs mainly in men who are older than 65 years of age and almost exclusively among uncircumcised men [2]. However, it has also been reported among men who had been circumcised as newborns with a history of penile infection with the human papilloma virus (HPV). In fact, HPV infection is an aetiological agent of SCCP, and 30-60% of persons with SCCP are found to have been positive for HPV [3]. Regarding circumcision, it is generally accepted that it reduces the risk of SCCP, eliminating the possibility of phimosis and related chronic inflammatory conditions [3]. Scleroatrophic lichen (LSA) of the penis, in which frequent secondary phimosis causes chronic inflammation, is associated with a higher incidence of SCCP [4-6]. A relationship between smoking and SCCP has also been suggested [3].

SCCP predominantly affects the glans, followed by the prepuce, the coronal sulcus and, though rarely, the penile shaft. Histologically, SCCP can show various degrees of differentiation, from the more differentiated verrucous type to the anaplastic type without keratinization. Furthermore, the prognosis depends on the degree of invasivity and metastatization: the well-differentiated verrucous type has a low metastatic rate, whereas the other three clinicopathological types: superficially spreading, multicentric and vertical growth, are associated with an increasing tendency to metastasize [7].

The choice of treatment for SCCP depends on staging [8], and therapeutic guidelines have been proposed [9]. The first-line therapy is surgical resection, with assessment of surgical margins; however, because of the resultant functional loss and psycho-sexual consequences, conservative therapy is recommended, such as external beam radiotherapy (EBRT) and brachytherapy (BT), which can preserve both the morphology and function of the sexual organ. For *in situ* SCCP, other conservative techniques have been used, such as topical 5-fluorouracyl (5-FU), cryotherapy, laser ablation and Mohs surgery [1].

At the Sant'Eugenio Hospital, we have used dermo beta brachytherapy (DBBT) with 188-Re to treat patients with a histologically confirmed diagnosis of basal cell carcinoma and squamous cell carcinoma of the epidermis. With this method, a synthetic inert resin-matrix containing a radioactive beta-emitting isotope is applied to the surface of the tumour lesion, allowing for selective brachytherapy irradiation of the neoplasm, so that only the tumour lesion is subjected to brachytherapy irradiation. In all 53 cases treated to date, a clear clinical remission was achieved in approximately 3 months; during a follow-up of 20-72 months (mean: 51 months), no clinical relapses were observed and histological examination confirmed complete tumour regression [10]. In the present work, we used this technique to treat patients with a confirmed diagnosis of squamous cell carcinoma of penis

To cite this article: Carrozzo AM, Sedda AF, Muscardin L, Donati P, Cipriani C. Dermo beta brachytherapy with 188-Re in squamous cell carcinoma of the penis: a new therapy. *Eur J Dermatol* 2013; 23(2): 183-8 doi:10.1684/ejd.2013.1927

Materials and methods

The study population consisted of 15 Caucasian males, coming from the Dermatological Departments of the San Gallicano Institute and the Sant'Eugenio Hospital (Rome, Italy), in the period from June 2005 to April 2010. All the patients were affected by chronic genital inflammatory dermatosis and presented suspect neoplastic genital lesions. According to their medical history, these individuals had previously undergone unsuccessful topical therapy, which consisted of steroidal, antibiotic and hormonal creams; one patient (no. 12) had been treated with imiquimod and 5-fluorouracil, without success; another patient (no. 3) had undergone surgery for phimosis and one patient (no. 7) had undergone surgery three times for verrucous SCCP, which was unsuccessful in removing the tumour lesion. The men ranged in age from 31 to 92 years, with a mean age of 65.6 years.

The patients were submitted to skin biopsy, and histological examination revealed the following: nine cases of *in situ* SCCP (patients 1, 2, 3, 4, 9, 11, 12, 13, and 15); three cases of verrucous SCCP (patients 5, 6, and 7); one case of micro-invasive SCCP (patient 10) (*figure 1A*); and two cases of invasive SCCP (patients 8 and 14); in six of the fifteen men, a scleroatrophic lichen was present (patients 1, 3, 8, 11, 12, and 14).

Radiologic and ultrasound examinations revealed that none of the patients had metastatic disease. Based on the TNM Clinical Classification, we defined the tumor degree, nine as "Tis", three as "Ta", and three as "T1a" *(table 1)*.

A ready-to-use, certified brachytherapy kit (Re-SCT TM, ITM, Munich, Germany) was used to treat tumor lesions. The product basically consists of a synthetic resin matrix, in which a nanocolloid containing ^{188}Re beta emitting isotope is homogeneously distributed in fine dispersion. The isotope ^{188}Re is a mixed beta–gamma emitter with a half life of 16.98 hours and β-particles with a maximum energy of 2.12 MeV. The surface of the lesion was protected with a thin layer of a specially designed, flexible, adhesive plastic foil, to prevent direct contact of the radioactive matrix with the epidermis. The radioactive source was then applied on the tumour lesion, above the protective plastic layer, using a specially designed shielded ergonomic applicator, which contains the capsule with the radioactive matrix. After 5 to 10 minutes, the matrix solidified, without shrinkage; the radioactive mould was kept on the lesion for the time necessary to administer the predetermined dose *(figure 1B)*.

The administered dose depended on the initial activity of the isotope, the isotope emission energy, the application area and contact time. Due to the use of radioactive material, the brachytherapy treatments were performed at the Department of Nuclear Medicine.

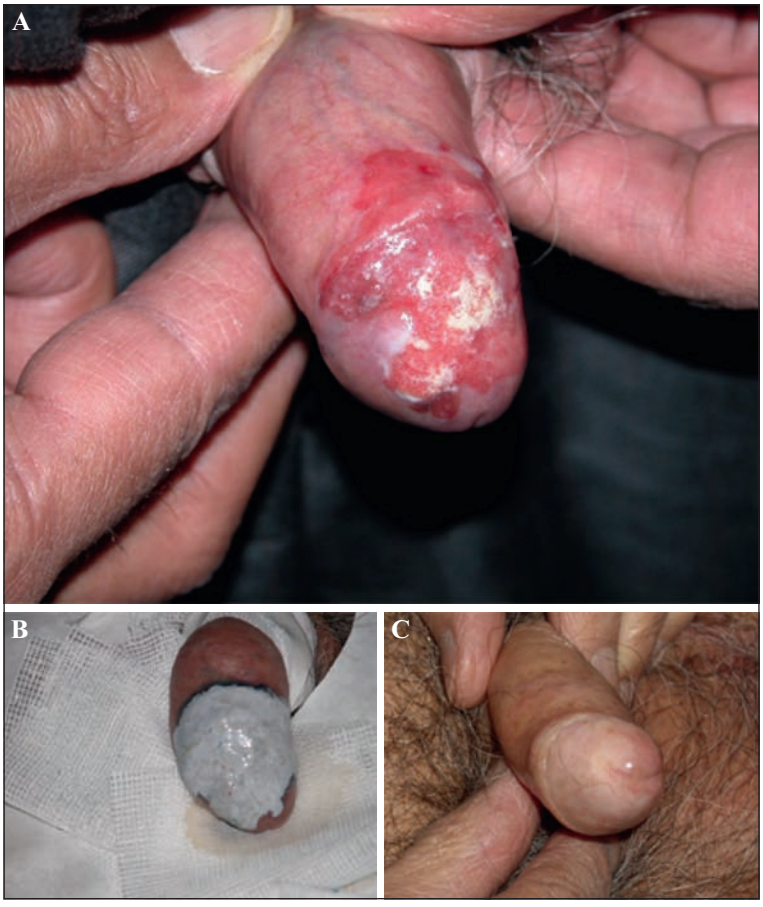

Figure 1. A) Microinvasive SCCP, (pat. N° 10). **B)** DBBT technique : radioactive mould applied on the glans, (pat. N° 10) **C)** successful result after three DBBT sessions, (pat.N° 10).

Table 1. Clinical cases.

Patient's Number (age)	Site (Histology) TNM Classification	Brachytherapy sessions (date)	Results (months follow-up)
1) G.G. (77)	Glans (*in situ* Sq Ca (with LSA) Tis	I (29 January 2010) II (25 November 2010)	LFU
2) D.A (92)	Glans *in situ* Sq Ca (Queyrat) Tis	I (25 July 2008)	AWD (26) Dead from other causes
3) G.A. (47)	Glans (*In situ* Sq Ca with LSA) Tis	I (24 October 2007) II (2 April 2008) III (8 February 2009)	AWD (52)
4) M.P. (31)	Glans (*In situ* Sq Ca, Queyrat) Tis	I (12 March 2008)	AWD (48)
5) M.F. (86)	Glans (Verrucous Sq Ca) Ta	I° (27-10-2008)	AWD (40)
6) M.A. (75)	Glans (Verrucous Sq Ca) Ta	I (2 December 2009)	AWD (26)
7) S.F. (70)	Glans (Verrucous Sq Ca) Ta	I (5 March 2008) II (26 May 2008) III (10 January 2010)	NR (24)
8) Z. D. (67)	Glans (Sq Ca with LSA) T1a	I (8 June 2009)	NR (12)
9) A.F. (40)	Glans (*In situ* Sq Ca Bowen, multifocal) Tis	I (30 July 2007) II° (9 June 2008) III (27 October 2009)	AWD (56)
10) S.G.(72)	Glans (Sq Ca microinvasive) T1a	I (19 September 2007) II (10 March 2008) III (17 January 2010)	AWD (54)
11) P.S. (77)	Penile shaft (*in situ* Sq Ca with LSA) Tis	I (19 January 2007)	AWD(58)
12) D.G. (70)	Glans (*In situ* bowenoid Sq Ca with LSA, multifocal) Tis	I (22 June 2005) II (3 October 2005) III (5 February 2007) IV (9 July 2007) V (10 March 2008) VI (10 February 2009) VII (25 October 2009)	AWD (84)
13) T.M.F. (69)	Glans (*In situ* Sq Ca , Queyrat) Tis	I (21 July 2008) II (17 November 2008)	AWD (40)
14) G.M. (76)	Glans (Sq Ca with LSA) T1a	I (19 April 2010) II (9 May 2011) III (10 November 2011)	AWD (24)
15) P.M. (35)	Glans (*In situ* Sq Ca Bowen) Tis	I (3 December 2007)	AWD (51)

AWD (alive without disease), R (relapse), LFU (lost to follow-up), NR (non-responder)

The area to be treated was framed by a dermographic pen, using accurate visual and dermoscopy examination, and the area of the lesion was measured. The irradiation field included both the area of evident infiltration and the peripheral neoangiogenic zone. An apparently healthy tissue border of 2-4 mm was also included in the irradiation field. For each patient and each lesion, the dose-distribution curve was calculated using a modified multi-point source real-time integration software program (Varskin2), which was validated by comparing the results with an independent Montecarlo calculation. At the end of the irradiation time, which ranged from 30 to 60 minutes, the radioactive mould was easily removed using specially shielded tongs, and it was discarded as radioactive waste.

Immediately after treatment, a faint redness of the treated area was visible. After a few days, this erythema was still present, in three cases with secretion of serum, and after crust or scale were temporarily formed. After three to four months, visual clinical healing occurred *(figure 1C)*.
Three-four months after brachytherapy, clinical evaluation, with dermoscopic and histological evaluation, was performed; clinical evaluation was then performed twice a year, for up to five years after treatment.

Results

The results for the 15 patients were as follows: twelve patients showed complete remission of the tumour (numbers 2, 3, 4, 5, 6, 9, 10, 11, 12, 13, 14, and 15); two patients (numbers 7 and 8) did not respond to therapy and were submitted to surgical salvage therapy; and one patient (number 1) was lost to follow-up. The mean duration of follow-up was 51 months. Of the seven patients who underwent a single DBBT session (patients 2, 4, 5, 6, 8, 11, and 15), only patient 8 did not respond; this was the only patient with invasive SCCP. Of the six patients who responded after a single session of DBBT, four had *in situ* SCCP (patients 2, 4, 11, 15) and two had verrucous SCCP (patients 5, 6). Two patients (patients 1 and 13), both with *in situ* SCCP, required a second session of DBBT; patient 1 did not return for the second session and patient 13 showed complete remission of the tumour. Five patients required three sessions (patients 3, 7, 9, 10, and 14), among these, only patient 7 did not respond to treatment. While patients 3, 7, 10 and 14 were treated on the same area in different sessions, for patient 9, each session was performed in a different site because of the multifocality of the neoplasm. One patient (patient 12) was submitted to seven sessions in different areas of the glans, because of the multifocality of the neoplasm *(table 1)*. The technique was completely painless, and none of the patients had any disconfort or collateral effect from the therapy.

Discussion

As reported above, in six of fifteen patients (40%) a sclero atrophic lichen was also present. Many studies have confirmed the relation between LSA and SCCP [4-6]. In particular, two types of retrospective studies have been performed: the first is based on the analysis of a large series of LSA patients, searching for the presence of penile tumor lesions, and a percentage of 8.4% for malignant transformation has been described [4]; in another study the percentage was 5.8%, all but one of these cases had associated HPV infection [11]. The second type of study looked for evidence of LSA in patients with CP: 40% positivity for LSA was found [12]. Both types of study confirm the relation between LSA and CP. Likewise, in women affected by vulvar sclero atrophic lichen, the association with vulvar carcinoma is well known and the pathogenetic mechanism is supported by chronic inflammation and scarring, which predispose keratinocytes to neoplastic initiation with oxydative damage of DNA [6]. Of course not all patients with vulvar and penile LSA develop a carcinoma, given that other factors play a role in this multifactorial cancerogenic process, such as HPV infection, exposure to environmental carcinogens and individual susceptibility.
With regard to therapy, for carcinoma *in situ* (Tis), non-invasive verrucous carcinoma (Ta), and tumours invading subepithelial connective tissue (T1a) (low-grade, G1 and G2), a conservative treatment can be recommended, such as laser therapy, photodynamic therapy, topical 5-FU, limited surgical approach, up to radiotherapy procedures such as external-beam-radiotherapy (EBRT) and brachytherapy (BT) [1]. For invasive cancer, including T1b/G3 and T2, surgery with margins of 15-25 mm demonstrates an excellent local control rate [13]; for superficial tumours (T1), to preserve the morphology and functioning of the organ, limited excision with a margin of a few millimetres has shown good results, and Mohs surgery can help to limit the extent of resection [14].
A conservative strategy using EBRT or BT is becoming increasingly popular, given that these techniques allow the morphology and functioning of the penis to be preserved; however, they should only be performed in carefully selected patients whose tumors encompass less than half of the glans and for whom close follow-up can be performed [9]. Quality of life and sexual function are important issues that tend to lead to the adoption of a non-surgical approach: both EBRT and BT are locally effective and allow amputation to be avoided. EBRT is generally administered with a 2-Gy-daily fraction, for a total dose of 60-66 Gy in 6-6.5 weeks, using two opposite beams. BT is a radiotherapeutic method in which the source of radiation is placed at a short distance (the term "brachy" is Greek for "short"), directly on or in the target tissues (intracavity, transluminal, interstitial). BT is categorized as low dose rate (0.4-2 Gy/h), medium dose rate (2-12 Gy/h), or high dose rate (greater than 12 Gy/h).
Classic BT is recommended for tumor T1 and T2 <4 cm in diameter, with <1 cm of invasion margin. In classical BT, 2 or 3 parallel rows of needles are inserted into the glans, with total or regional anaesthesia, in accordance with the "Paris system" protocol [15, 16]. The needles are manually loaded with iridium-192 and the median dose is 65 Gy, delivered at a rate of 50-65 cGy per hour, with 100-120 hours (4-5 days) of total duration of the implant with uretral catheter. Classic BT has been shown to result in a 5-year local tumor control rate of 70-86% and a penile preservation rate of 72-83%; recurrences after classic BT, which may also include new primary tumors, require surgical salvage (partial or total penectomy), which has shown good results; classic-BT has better survival results than EBRT [16].
A less invasive BT technique is the HDR-surface-mold brachytherapy and mostly gamma-emitting isotopes, such as 192-Ir, have been used [17]. Beta emitter isotopes such as holmium-166 [18] or, more recently, rhenium-188 (DBBT) [10] have been used in tumours of the skin with excellent results [19].
X-ray beam therapy, gamma photon radiotherapy and classic BT can all cause side effects in underlying tissues because of their penetrating nature: by contrast, DBBT consists of a highly selective surface beta radiotherapy of the tumour lesion. The high energy (>1MeV) electrons from beta emitter isotopes are therapeutically effective only at a

short distance and they allow underlying healthy tissue to be spared. As a matter of fact, beta radiation deposits more than 90% of the dose in the first two mm of the skin, which is the depth usually involved in superficial tumor invasion. In the patients described herein, the beta emitters were distributed (see Materials and methods) in a matrix that was able to adapt to every skin surface, with an accurate distribution of dose on one or more lesions, sparing healthy tissue [10].

Unlike classic BT with gamma emitters and needle-implants, DBBT does not require that the patient be hospitalized; it lasts 30-60 minutes and does not require invasive procedures, it can be repeated, and it is indicated for carcinoma *in situ* (Tis), verrucous non-invasive carcinoma (Ta) and for initial invasive carcinoma (T1a), which invades "subepithelial connective tissue without lymphovascular invasion, until histologic grade G2" [8], in fact the beta-emitter isotopes are active in the first two millimeters of the skin. In invasive carcinoma of penis from T1 until T4, the thickness of tumour has to be carefully defined, in fact microinvasive carcinoma (T1a) can be eligible for DBBT, up to a thickness of 2-3 mm, on the contrary, in invasive carcinoma with a greater tumour thickness, an alternative therapy must be used, from surgery to classic BT with needles or EBRT.

A patient real case dose absorption curve in human tissue for the beta emitter 188Re is reported in *figure 2*. It should be pointed out that the mean dose distribution curve corresponding to performed treatments shows a clear decrease in the dose, from a nominal value of about 80 Gy in the epidermis to less than 10 Gy at a depth of only 2 mm, a depth seldom involved in invasion in these types of tumours. The dose distribution curve obtained by the use of beta particle irradiation apparently seems to ideally "follow" the distribution of the tumor invasion in the dermal tissue, administering the therapeutic dose only at the required depth, without unnecessary dose deposition in the subdermal tissue. The choice of the apparently healthy tissue to be included in the irradiation is an important parameter, because a lethal dose must be administered to the potentially infiltrating cells in the external border.

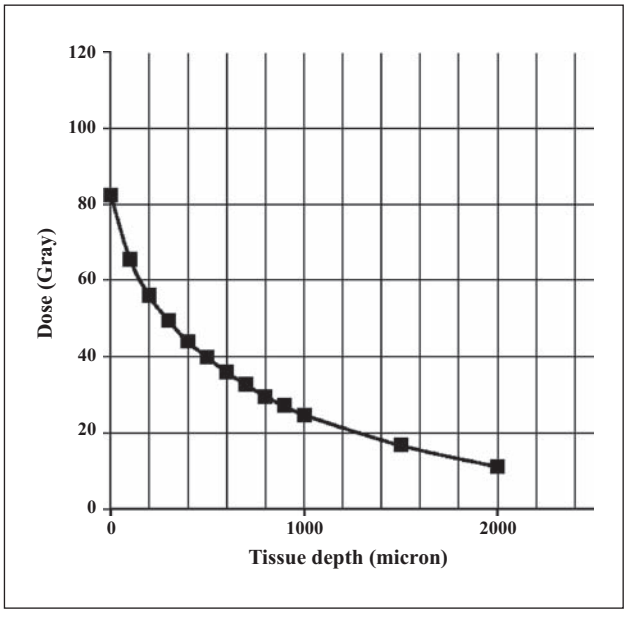

Figure 2. Dose absorption curve in human tissue for the beta emitter 188-Re.

The present paper is the first report of DBBT in penile cancer and the clinical results are quite promising. The technique is therefore proposed as a therapeutic choice in superficial carcinoma (up to T1a with low thickness), not only an alternative to medical treatments, but also to surgery. The technique is rapid and safe, and the treatment is mostly performed in a single therapeutic session, without discomfort for the patient. ■

Disclosure. *Financial support: none. Conflict of interest: none.*

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