

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

Cesidio Cipriani^{1,2,*}, Benjamin Frisch³, Klemens Scheidhauer⁴ and Maria Desantis¹

¹*AlGa Institute for Nuclear Medicine, Via Stazione 5-11, 67043 Celano (AQ), Italy*

²*Nuclear Medicine Division, Casa di Cura Madonna della Fiducia, Via Alfredo Baccarini, 54, 00179 Rome (RM), Italy*

³*Computer Aided Medical Procedures (CAMP), Technische Universität München, Boltzmannstr. 3, 85748 Garching bei München, Germany*

⁴*Nuclear Medicine Department, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675 München, Germany*

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, Palladium-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].

*Address correspondence to this author at the AlGa Institute for Nuclear Medicine, Via Stazione 5-11, 67043 Celano (AQ), Italy; Tel: +39 3291713541; Fax: +49 89 54842249; E-mail: cesidiocipriani@gmail.com

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 cumbersome 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 detected by 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 Tеча river cohort, Strontium-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

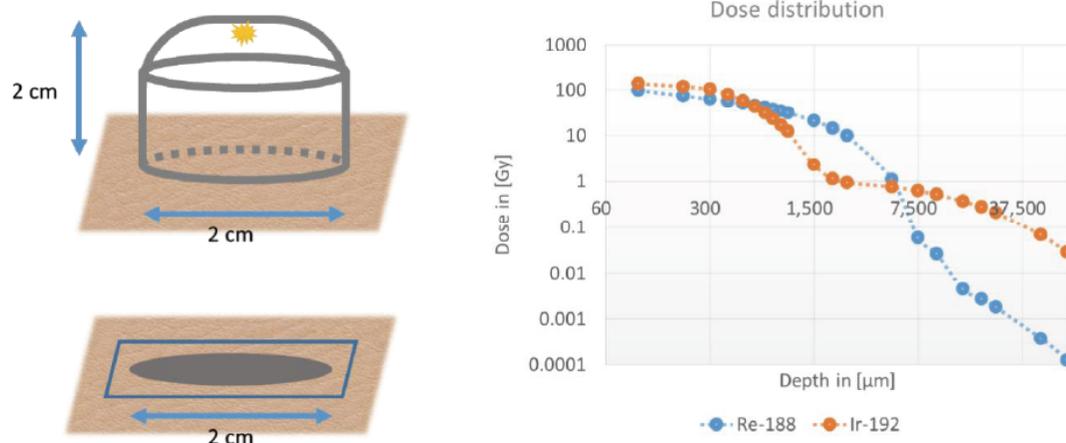


Figure 1: Right, dose at different skin depth for Rhenium-188 versus Iridium-192 for a comparable total dose of 65 Gy within the first 1.5mm. Simulations were performed using NRC's VARSKIN 5.2 software [14]. Left, schematics of simulated scenarios with VARSKIN.

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-

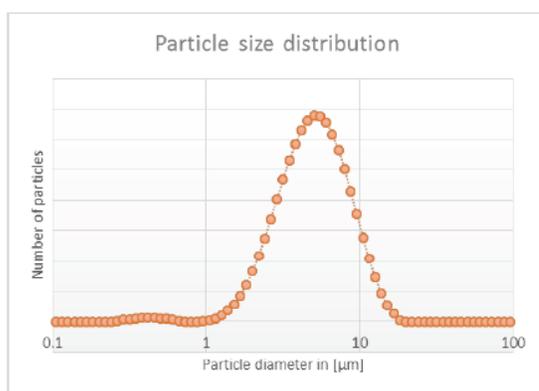


Figure 2: Left, particle size distribution of dirhenium-heptasulfide from our production. Right, scanning electron microscope image of dirhenium-heptasulfide particles (round).

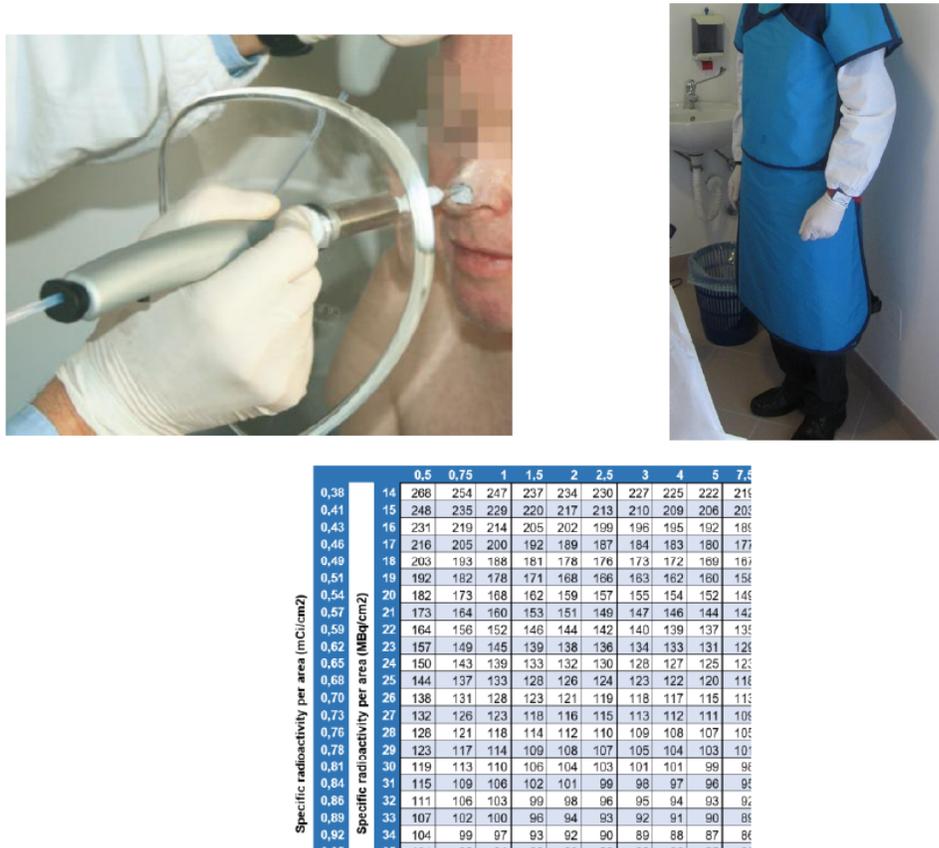


Figure 3: Top left, tool for application of radioactive matrix on patient during a procedure. Bottom left, table used for calculation of treatment time for a given target depth (here a protocol of 50 Gy to 300 µm). Right, physician fully equipped with radiation protection clothes.

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 cm².
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 the application 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, epiluminescence images were 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.

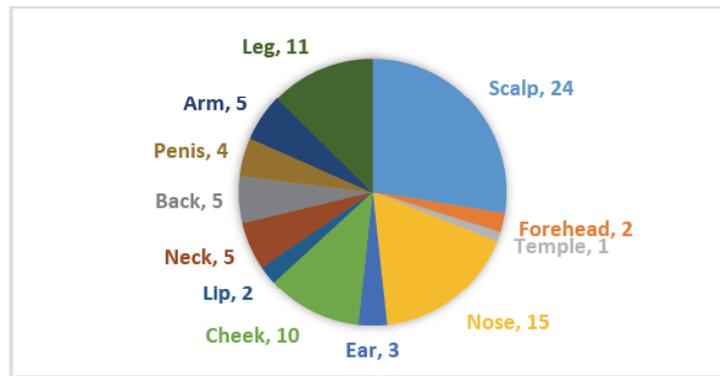


Figure 4: Distribution of lesion localization within the 43 patients.

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 cm² and 49 cm² (single lesion), in average the area treated was 5 cm² with a median of 3 cm² (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

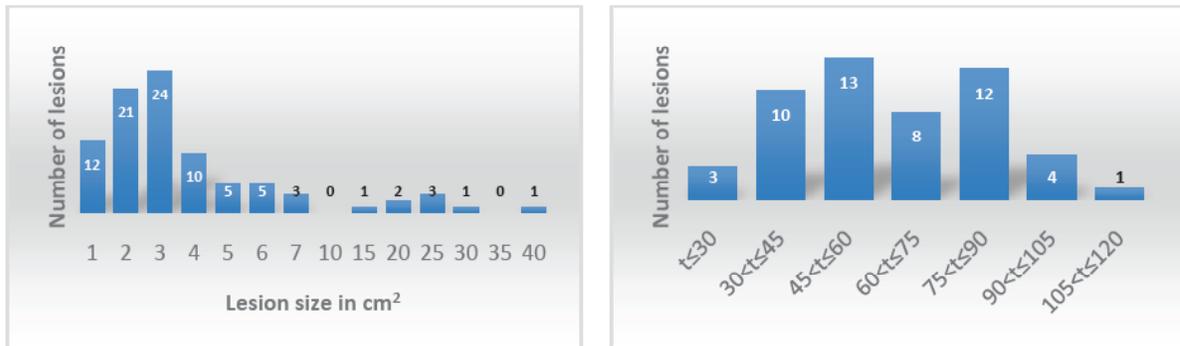


Figure 5: Left, histogram of lesion size for all 88 lesions. Right, histogram of treatment times for all 49 treatments (37 single treatments and 6 double treatments).

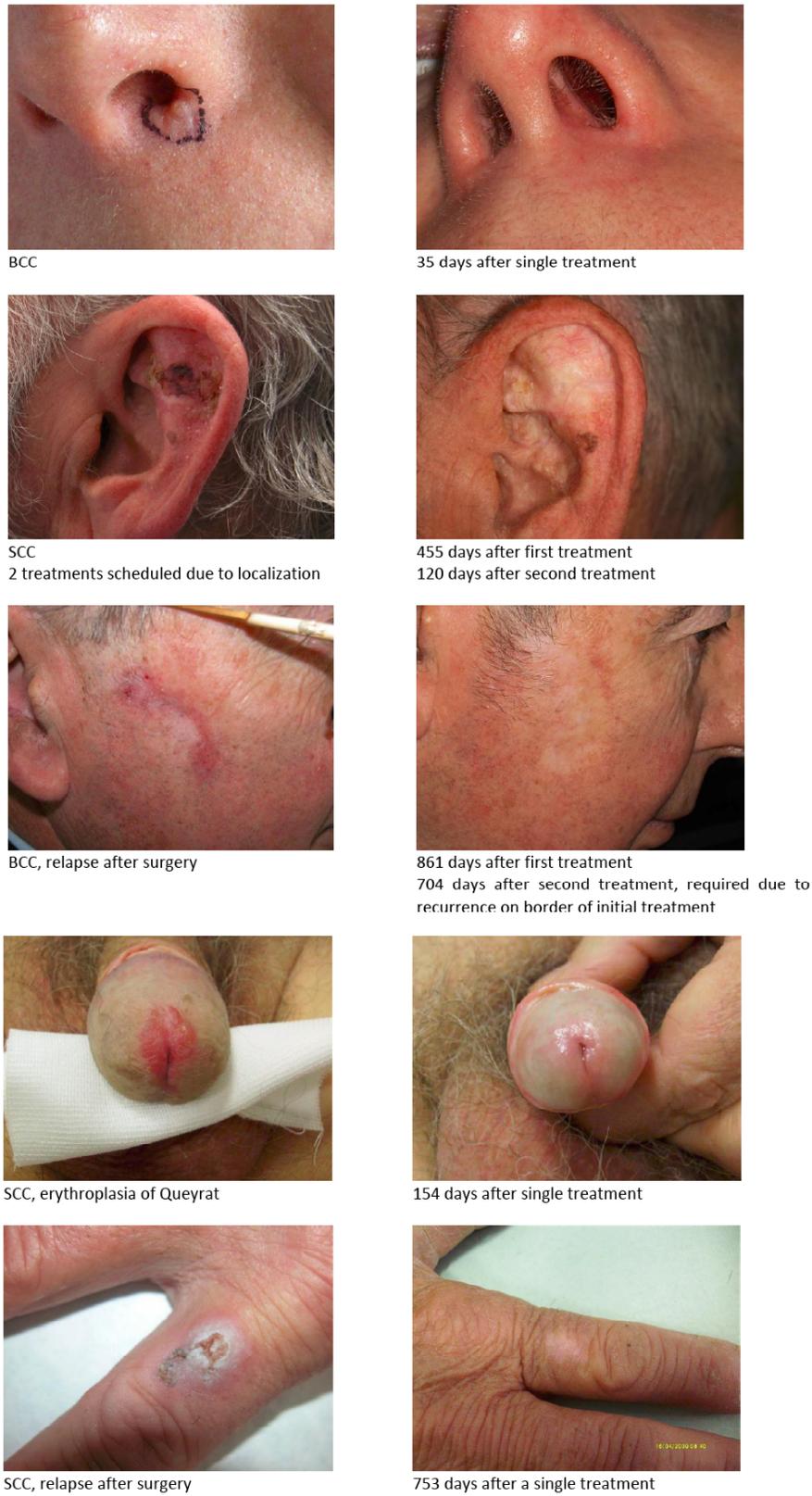


Figure 6: Examples of lesions treated before and after the brachytherapy with Rhenium-188.

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.

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