Dermatology Practical & Conceptual

Unsealed ^{188}Rhenium Resin Brachytherapy in Non-Surgical Candidates With Refractory Basal Cell Carcinoma: Clinical Outcomes

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ABSTRACT

Introduction: High-dose brachytherapy using a non-sealed ^{188}Rhenium resin (^{188}Re) is a new treatment option for difficult-to-treat basal cell carcinoma (BCC) that ensures a radical oncological outcome minimizing side effects.

Objectives: The aim of this retrospective study was to evaluate the clinical efficacy of high-dose standardized brachytherapy using an unsealed ^{188}Re in the management of difficult-to-treat BCCs and to evaluate the risk factors of relapses.

Methods: Between October 2017 and December 2022, patients affected by difficult-to-treat BCC were selected. Inclusion criteria: histologically proven cutaneous BCC; thickness invasion no deeper than 3 mm; lesion located in the scalp, face, ears, or fingers or other areas in which surgery would have been difficult to perform or to destroy with scarce cosmetic-functional result; contraindication or refusal of surgery. All patients performed follow-up visits with videodermoscopy every 4–6 months.

Results: Sixty-four consecutive patients affected by 82 histologically proven high-risk BCCs, were enrolled: 60 were nodular, 9 sclerodermiform, and 13 superficial. Average follow-up was 24 months. Brachytherapy with ^{188}Re resin achieved a complete response in 93% of "difficult-to-treat" BCCs, with relapses occurring on average 24 months after the initial treatment.

No statistically significant difference in response to brachytherapy was found in the anatomical area treated, size of the tumor, or previously treated vs. naive BCCs. The sclerodermiform histotype had a 7-fold higher risk of recurrence than nodular histotype; recurrence occurred approximately 12 weeks earlier.

Conclusion: High-dose ^{188}Re brachytherapy is a noninvasive, easy to perform, well-tolerated approach to treat difficult BCC when surgery or other therapy techniques are not feasible.

Introduction

Non-melanoma skin cancers (NMSCs) represent the most common form of cutaneous cancers in humans, accounting for approximately 80% of all diagnosed cases [1]. Basal cell carcinoma (BCC) accounts for approximately 80% of NMSC diagnoses per year, as reported by the American Cancer Society [2].

Accordingly, more than 3 million patients, especially older adults, receive treatment each year, and about 5% of these patients are diagnosed with an advanced stage of the disease, showing a high locoregional recurrence risk [3]. The goal of the treatment of BCC, according to the National Comprehensive Cancer Network (NCCN), is to achieve complete cure and the highest preservation of function and cosmetics. [4] Early treatment of common BCC is curative in the vast majority of cases, and surgical excision is the first-line treatment in most cases [5] The European Association of Dermato-Oncology (EADO) classification divides BCCs into two categories, "easy-to-treat" (common) and "difficult-to-treat"[6]. More than 90% of BCCs are easy to treat through standard surgery or a range of alternative treatments during the initial months or years after diagnosis. Difficult-to-treat BCCs include all BCCs which, for any reason, pose specific management difficulties. Six main reasons were classified by Peris et al. [7] defining a BCC as difficult-to-treat because of: (1) technical difficulty of maintaining function and aesthetics due to the size or location (eyes, nose, lips, and ears) of the tumor; (2) poorly defined borders often associated with the sclerodermiform (sd) subtype or with a recurrence; (3) multiple recurrences on the face (often requiring much larger excision); (4) prior radiotherapy; (5) patient's reluctance to accept the consequences of surgery; (6) patient's comorbidities interfering with surgery. For the NCCN, the key risk factors for high-risk BBCs include tumor localization (especially in the head and neck), size (>6 mm in high-risk area and >10 mm in moderate-risk area), concomitant immunosuppression or prior radiotherapy, poorly defined borders, recurrent disease, and aggressive histopathological subtypes [8]. While surgery, particularly Mohs micrographic surgery, remains the gold standard for difficult BCC treatment, radiotherapy (RT), including brachytherapy, is a viable option for carefully selected patients with contraindications to surgery or those who decline surgical treatment. In recent years, brachytherapy with ^{188}Re has been approved in Europe, and high-dose brachytherapy using an unsealed ^{188}Re, commercially identified as the medical device Rhenium-SCT (Oncobeta GmbH), offers a novel approach that allows radioactivity to be delivered as closely as possible to the entire surface of the lesion regardless of its shape and three-dimensional volume This brachytherapy approach exploits the properties of ^{188}Re to release high-energy (Beta (β) 2.2 MeV; Gamma (Ɣ) 155KeV: emission 85% β and 15% Ɣ radiation) in the superficial layers of the skin. Finally, it is noteworthy that ^{188}Re physical characteristics are ideal for brachytherapy since about 75% of its energy is delivered within 1 mm and 92% within 3 mm of depth, and only a negligible amount of energy is delivered below 3 mm. High-dose rate brachytherapy using iridium-192 (^{192}Ir) or unsealed ^{188}Re-resin as a source for the treatment of skin cancers reported 98% efficacy up to five years of follow-up, excellent treatment tolerance, and no serious early or late complication [8-14]. Brachytherapy with ^{188}Re could be a tailored solution in situations where (a) surgery or external beam radiation or other brachytherapy approaches could produce suboptimal results due to the location, size, or potential cosmetic outcome of the lesion after surgery; (b) the patient's general health and comorbidities make him/her unsuitable for surgery; and (c) patients forgoing surgery. Several studies reported in the literature have evaluated the clinical efficacy of brachytherapy with ^{188}Re or ^{192}Ir without stratifying BCCs by histological type, size, and anatomical location[9,] [11-16].

Objectives

In this retrospective study, we wanted to deepen and enrich with more data a previous work of our center in which we

described the first results of our first experience on the application of brachytherapy with non-sealed ^{188}Re in 50 consecutive patients with non-melanoma skin cancers [13]. The primary endpoint was to evaluate the clinical efficacy of a single application of high-dose standardized brachytherapy using an unsealed ^{188}Re in the management of difficult-to-treat basal cell carcinoma. The secondary endpoint was to evaluate the risk factors of recurrences and the timing of the recurrence after brachytherapy considering the following features: (1) the histological type of the BCC, (2) the size of the BCC, (3) the anatomical area involved, and (4) recurrent vs. naive BCC.

Methods

Inclusion Criteria and Reference Standards

The study was performed according to the Helsinki Declaration; patients signed written informed consent to participate, and the study was approved by local Ethics Committee (23/2019/Oss/AOUBo). Between October 2017 and December 2022, patients affected by difficult-to-treat BCC (including both new diagnosis and relapses) were selected by the Dermatology Unit and Nuclear Medicine of the Azienda Ospedaliero-Universitaria di Bologna, Sant'Orsola-Malpighi Hospital. Inclusion criteria of our study were: (1) histologically proven cutaneous BCC; (2) lesion thickness invasion not deeper than 3 mm (arbitrary cutoff based on ^{188}Re characteristics) according to single or multiple diagnostic biopsies; (3) the presence of one or more criteria to define a patient with difficult-to-treat BCC [7]. Of the 152 lesions treated with Rhenium-SCT since October 2017, 64 consecutive patients affected by 82 histologically proven difficult-to-treat BCCs were included in this study. Shared decision-making was a key part of the treatment program, and the treatment choice reflected patient preference when surgery posed risks or was not preferred. Patients were fully informed of surgical options and non-surgical alternatives, including brachytherapy with the non-sealed ^{188}Rhenium (^{188}Re) resin for those who opted for a less invasive treatment.

Patient Stratification

The BCCs selected were all histologically confirmed and grouped into the following three histological subtypes: superficial, nodular, and sclerodermiform. According to the literature, skin areas involved were stratified into high, medium, and low risk [16-17]. Area "H" included lesions of any size located in the central part of the face, eyelids, eyebrows, periorbital area, nose, lips, chin, jaw, preauricular area, temporal area, ears, genitals, hands, or feet. Area "L" included lesions located on the trunk and extremities, excluding hands and feet. Area "M" consisted of lesions on the cheeks, forehead, scalp, neck, and pretibial region. For all BCCs included, the cutaneous extension was specified in cm^2. Twenty out of 82 recurrent cutaneous BCCs from previous treatments were also included: three BCCs had already been treated with surgery, six BCCs with photodynamic therapy and cryotherapy, 10 BCCs with cryotherapy, laser, and photodynamic therapy, and one BCC with imiquimod 5% cream.

Follow-Up With Videodermoscopy

Clinical and dermoscopic photographs before and after treatment were recorded with FotoFinder Vexia (FotoFinder Systems GmbH). All patients included in the study performed follow-up visits with videodermoscopy every 4–6 months at the skin cancer unit of the Azienda Ospedaliero-Universitaria di Bologna, Sant'Orsola-Malpighi Hospital. Patients were classified as complete responder (CR) if the videodermoscopy did not show any suspected area of relapse of the disease or if the biopsy guided by the dermoscopy resulted as negative or as non-responder (NR) in cases of relapses of disease evidenced by a positive histological examination. The average follow-up of the patients included in the study was 24 months (range 2–24 months). The relapse rate was considered throughout the follow-up period.

Standard of Treatment With ^{188}Re-Based Resin Application

The application of high-dose brachytherapy with unsealed ^{188}Re resin followed the same procedure described in our previous papers [13-14].

Statistical Analysis

Data are summarized as median and interquartile range or absolute number and percentage, as appropriate. Between-group comparisons were performed through Mann-Whitney or chi-squared tests depending on the data. The survival time was calculated on an individual basis as the weeks spanning from treatment to relapse or last observation. To assess the relationship between time to relapse and characteristics of BCC (histological type, anatomical site affected, size and previous treatments) univariate and multivariate Cox analyses and restricted mean survival time (RMST) analyses were adopted to estimate the treatment effect. RMST is defined as the area under the survival function curve up to a specific time (t*). When the median survival time is not calculable because event-free survival does not cross the 50% cutoff, the mean survival time, or the mean time to event, provides useful information about the time to event. Furthermore, the difference in RMST (ΔRMST) describes the change (gain or loss) in event-free survival time between groups during a specific time frame. In Cox models, data are expressed as hazard ratio (HR), 95% confident

intervals (CI) and $P<0.05$ for statistical significance. Statistical analyses were performed with the survRM2 and temporal packages in the software R, version 3.6.3.

Results

Epidemiological Features

Between October 2017 and December 2022, 64 consecutive patients, including 40 (62.5%) males and 24 (37.5%) females, affected by 82 histologically proven high-risk BCCs were enrolled; age ranged from 52 to 97 years, mean 81 years (Table 1). The average age of the patients was 81.6 years at the time of the treatment, and the peak of age according to frequency distribution was the eighth decade.

Basal Cell Carcinomas Characteristics

Of the 82 lesions included in the study, 13 were superficial BCCs, 60 were nodular BCCs, and nine were sdBCCs, which included difficult-to-treat areas (such as the H area of the face) that would have required extensive surgical interventions (Figure 1). Three patients suffering from locally advanced BCC relapsed after surgery and were treated with brachytherapy with ^{188}Re to eradicate the BCC, with good cosmetic outcome (Figure 2). The H area was the most affected one (41/82, 50%), and the nose was the most common site of incidence, followed by the cheek. High incidence rates were also found in the M area (27/82, 32.9%). The L area showed the lowest incidence rates (14/82, 17,1%). Mean size area of the lesions was 5.96 cm^2 (min 1- max 31). The most represented size range was between 1 and 4.9 cm^2 (Table 1).

Relapse at Follow-up

All lesions that at follow-up with videodermoscopy were found to be suspicious for BCC relapse were subjected to multiple skin biopsies. After six months of follow-up, nine lesions suspected of relapse at dermoscopy showed arborizing-like vessels in the previously treated areas (Figure 3. Cancer cells were not found at histopathological examination (false positive) in 3/9 patients, while 6/9 suspected BCCs turned out to be true recurrences, highlighting the difficulty in differentiating arborizing-like vessels due to scarring (Figure 3A-F) from true arborizing vessels due to a relapse (Figure 3G-I).

Risk Factors of Relapses

In our sample, 23% (N=19) of lesions had already been treated without any significant association with subtype or location, nor with thickness or area treated; no statistically significant difference in relapse rate to brachytherapy was found in terms of the anatomical area treated, the size of the tumor, and the multi-treated BCCs compared to naive ones. On the contrary, different responses to treatment with brachytherapy were found in relation to the histological type. No recurrence was found for lesions of the superficial histological subtype (100% efficacy). However, a statistically significant difference was found between nodular and sdBCC (P=0.03) (Table 1). In fact, 3/9 (33%) sdBCC had recurrences compared to only 3/60 nodular BCCs (5%) (Table 1). Brachytherapy with the application of ^{188}Re resin achieved a complete response in 93% (76/82) of treated BCCs, and only six recurrences were observed, with a mean time to recurrence of 102 weeks or 24 months (95% CI: 98.4–105.7) (Figure 4). The univariate RMST and Cox survival analysis did not show any significant difference in the mean survival time nor in the hazard ratio (HR) for all the variables except for the histologic subtype (nodular VS sdBCC). In this case, the HR for relapse of the sd histotype is about six times higher than that for the nodular type. SdBCC show a time to first relapseof about 90 weeks, while for the nodular one is 102 weeks (Table 2). Subsequently, amultivariate nalysis was performed, adjusted by known principal risk factors, histologic subtype, and its recurrence and location, on the subset of sd and nodular BCC (69 lesions). Results show that compared to the nodular subtype, the sd subtype had a seven-times higher risk of relapse (Cox model HR 7.2), and relapse occured about 12 weeks earlier than in the other group (ΔRMST) (Table 2).

Conclusions

The aim of this study was to enhance and substantiate with additional data a prior investigation from our center, wherein we detailed the preliminary outcomes of high-dose brachytherapy using an unsealed ^{188}Re resin, Rhenium-SCT for NMSC. The focus was on locally advanced BCCs, with an expanded sample size and extended follow-up duration.

Dermoscopic Cutaneous Features after Brachytherapy

Throughout the follow-up, we observed multiple dermoscopic manifestations indicative of potential local recurrence. Specifically, nine lesions exhibited the arborizing vessels and sclerotic skin areas characteristic of BCCs, hinting at a potential dermoscopic indication of relapse [18-20]. Consequently, biopsies were performed on these areas of concern, with only six out of the nine lesions being histologically verified as BCCs. We think that local inflammation and the subsequent scar tissue due to the brachytherapy can be considered primary contributors to neo-angiogenesis and to the emergence of these arborizing-like vessels [21-25]. To better distinguish signs of relapse, confocal microscopy might be useful [26-27].

Table 1. Baseline Characteristics of Patients and of Lesions, Global and by Relapse. Chi-squared for Categorical Variables and Mann-Whitney for Continuous Variables.

	All (82)			No Relapse (76)			Relapse (6)			
	N (%)	Mean (SD)	Median (IQ)	N (%)	Mean (SD)	Median (IQ)	N (%)	Mean (SD)	Median (IQ)	*P* Values*
F	30 (36.6)			27 (35.5)			3 (50)			0.48
M	52 (63.4)			49 (64.5)			3 (50)			
Age		81.6 (8)	82 (78-87)		81.4 (7.8)	81.5 (78-86.5)		85.2 (9.4)	86.5 (80-91)	0.26
Histologic subtype										
Nodular	60 (73.2)			57 (75)			3 (50)			0.03 performed only 0 vs 1
Sclerodermiform	9 (11)			6 (7.9)			3 (50)			
Superficial	13 (15.9)			13 (0)			0 (0)			
Location										
H	41 (50.0)			38 (50.0)			3 (50)			0.99 even when L and M were aggregated
L	14 (17.1)			13 (17.1)			1 (16.7)			
M	27 (32.9)			25 (32.9)			2 (33.3)			
Thickness (mm)		1.4 (0.7)	1.5 (1-2)		1.4 (0.7)	1.5 (1-2)		1.3 (0.7)	1.1 (1-1.6)	0.26
Area (cm2)		6 (6)	3.6 (2-7.3)		5.5 (5.3)	3.6 (2-7)		11.8 (11.2)	7.8 (3-19)	0.09
Previous treatment, yes	19 (23.2)			18 (23.7)			1 (16.7)			
Previous treatment, no	63 (76.8)			58 (76.3)			5 (83.3)			1.00

Abbreviations: SD = standard deviation.

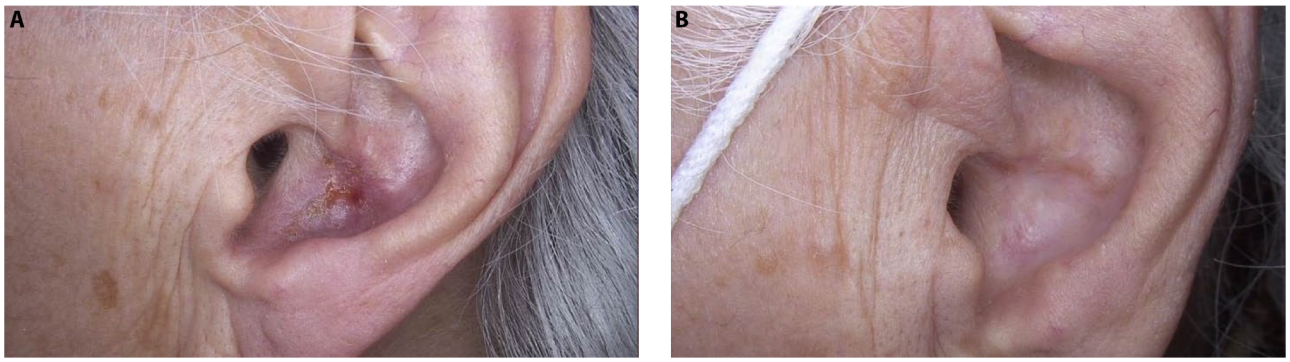

Figure 1. Sclerodermiform basal cell carcinoma of the auricle. (A) Before therapy and (B) six months after ^{188}Re brachytherapy.

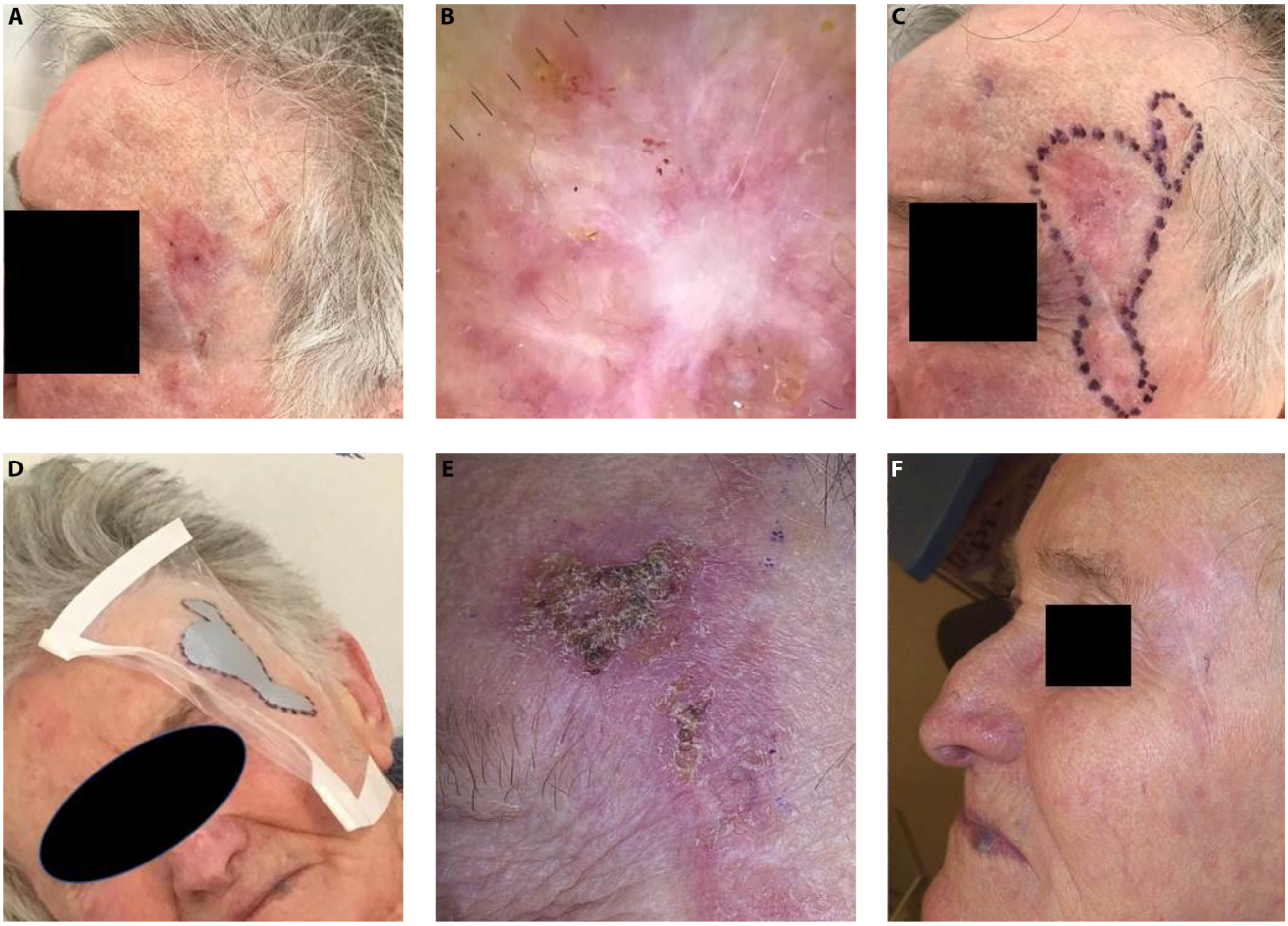

Figure 2. (A) Basal cell carcinoma (BCC) relapsed after surgery over and under the surgical scar. (B, C) Dermoscopy and demarcation of the cutaneous area before treatment with ^{188}Re brachytherapy. (D) Application of the ^{188}Re. (E) Four weeks post-brachytherapy, skin redness and scaling. (F) Complete healing with excellent cosmetic result after six months.

Efficacy of Brachytherapy

This is among the first studies in the literature that found statistically significant differences in relapse rates between the histological subtypes of BCC. In the literature there is a lack of data in relation to the efficacy of brachytherapy with ^{188}Re or ^{192}Iridium in difficult-to-treat BCC, stratifying the BCCs by histological type [10-13, 24]. In our sample there was no recurrence in patients with superficial BCC. These data are probably related to the greater effectiveness of the radioactive isotope on superficial lesions. On the contrary, the sd histotype showed a risk of recurrence six times higher than the nodular subtype and had an earlier recurrence time

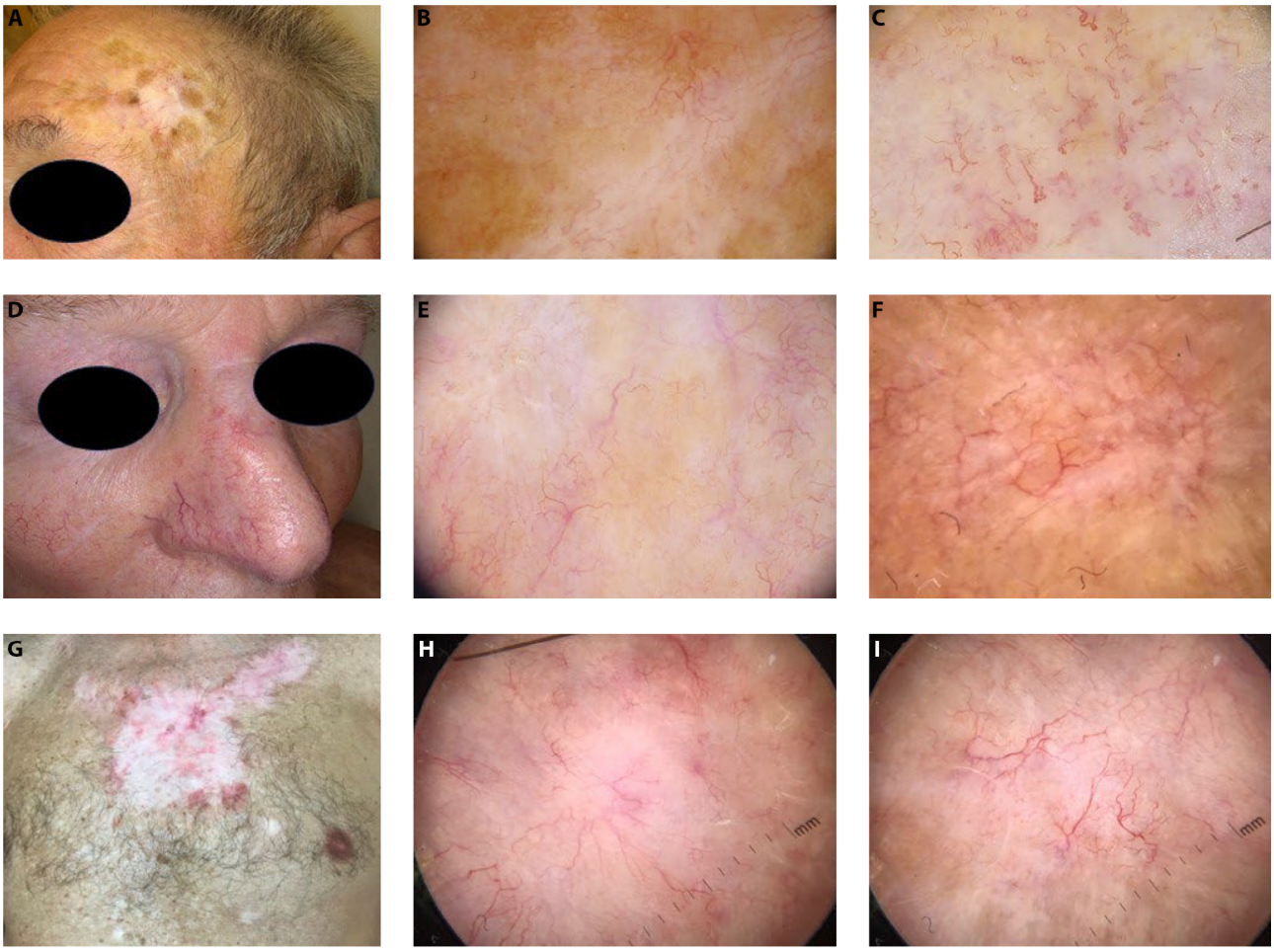

Figure 3. Clinical and videodermoscopy images at six months of follow-up after ^{188}Re brachytherapy. (A) Area affected by basal cell carcinoma (BCC) and treated with ^{188}Re. (B) Arborizing-like vessels can be seen. (C) Polymorphic comma, harpin, and linear-irregular vessels in other points. (D) Bridge of the nose affected by BCC. (E, F) At dermoscopy, arborizing-like vessels can be seen on a background characterized by erythema and skin sclerosis. (G) Patient with large basal cell carcinoma of the mid pectoral region. (H, I) On dermoscopy, arborizing vessels with focus are seen, suspicious of recurrent BCC.

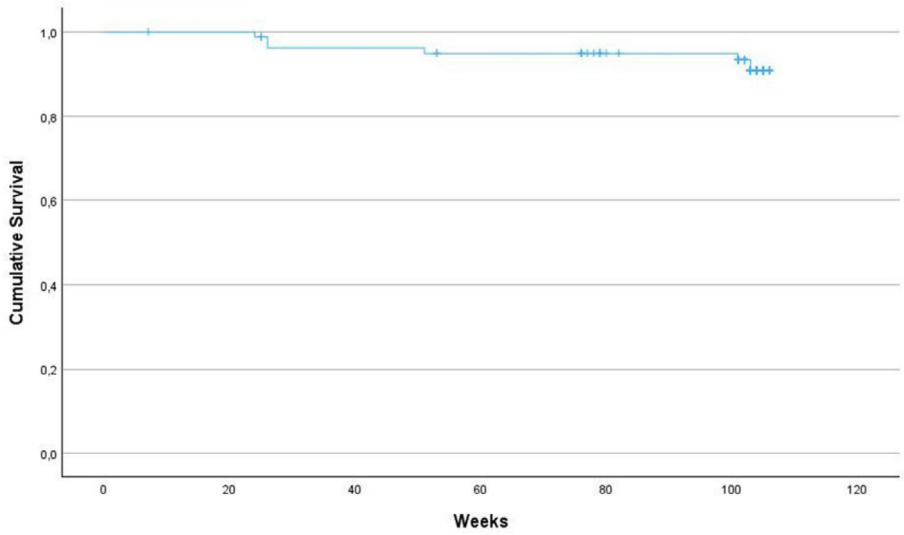

Figure 4. Kaplan curve with the average time free-from-relapses after brachytherapy.

Table 2. Univariate and Multiple restricted mean survival time (RMST) and Cox Analysis at 106 weeks.

	RMST 106 weeks	ΔRMST	*P* Value	Time Window	Hazard Ratio	*P* Value	Shoenfeld (*P* Value)
M	102.3 (99.3-105.4)	6.06 (2.86-14.98)	0.18	104 weeks	0.52 (0.11-2.60)	0.43	0.38
F	96.3 (87.9-104.6)						
Age >81	100.6 (94.7-106.4)	-3.08 (-10.27-4.11)	0.40	106 weeks	1.78 (0.33-9.72)	0.51	0.83
Age <=81	103.7 (99.5-107.8)						
Histologic subtype							
Superficial	nc						
Nodular	102.1 (98.3-105.9)						
Sclerodermiform	89.8 (71.4-108.1)	-12.36 (-31.08-6.36)	0.20	105 weeks	6.01 (1.21-29.93)	0.03	0.79
Location							
L	104.6 (103.7-105.4)						
M	99.8 (90.7-107.4)	-5.71 (-13.94-2.53)	0.17		0.93 (0.08-10.32)	0.96	0.19
H	101.6 (97.2-106.1)	-2.90 (-7.44-1.63)	0.21	105 weeks	0.88 (0.09-8.45)	0.91	
Thickness							
<1 mm	100.84 (92.91-108-77)						
1.0-1.4 mm	94.23 (80.63-107.82)	-6.62 (-22.36-9.13)	0.41	105 weeks	4.41 (0.46-42.6)	0.20	0.66
1.5-1.9 mm	102.65 (98.15-107.15)	1.81 (-7.31-10.93)	0.70		0.84 (0.05-13.52)	0.90	
=>2.0 mm	104.77 (104.32-105-21)	3.92 (-4.02-11.87)	0.33		0.89 (0.06-14.29)	0.94	
Size							
<3.7 cm^2	101.5 (96.69-106.31)						
=>3.7 cm^2	100.8 (95.40-106.19)	-0.71 (-7.93-6.52)	0.85	105 weeks	1.86 (0.34-10.19)	0.47	0.80
Previous treatments							
No	101.7 (97.3-106-2)						
yes	103.1 (97.6-108.6)	1.35 (-5.74-8.45)	0.71	106 weeks	0.57 (0.07-4.93)	0.61	0.76
Multiple models							
Nodular							
Sclerodermiform		-12.60 (-15.9- -9.3)	<0.001	105 weeks	7.27 (1.38-38.21)	0.02	0.41

Abbreviations: RMST = restricted mean survival time; ΔRMST = difference in MRST

of approximately 12 weeks. SdBCC is considered a difficult lesion to treat because it is characterized by deep tissue destruction and subclinical extension as well as by high rates of local recurrence [28]. Dermoscopy-guided biopsies performed pre-brachytherapy likely affected more superficial areas of the sdBCC histotype, but the lesion probably extended deeper than 3 mm in others skin areas. Regarding lesion edges, at clinical and dermoscopic examination, these appeared more frequently poorly defined in sdBCCs and more frequently well defined in nodular and superficial BCCs [28-29]; from this point of view, brachytherapy could not be performed in all cutaneous area affected by sdBCC.

Brachytherapy with ^{188}Re proved to be an extremely effective, fast, and painless method resulting in the healing of 93% of the difficult-to-treat BCCs included in the study at an average follow-up of 24 months, confirming the data previously reported in the literature [8, 11, 13, 20]. The method also made it possible to treat multiple lesions simultaneously in the same patient [11]. Moreover, we recommend a more rigorous follow-up regimen for the sdBCC compared to the nodular type.

Limitations

The study has two main limitations: (1) limited sample of patients affected by BCC, heterogeneous in size, histological type, and location of the BCC, (2) limited follow-up time; most BCCs (60%) recur after five years, so longer follow-up is needed [16-17], and (3) in our study there was no comparison with other treatment options.

Brachytherapy with ^{188}Re is an effective, rapid, safe, painless treatment and mostly performed in a single therapeutic session, regardless of the complexity of the form, anatomical location, and number of lesions. For these reasons this technique may emerge as a treatment modality in specific scenarios such as advanced patient age, comorbidities, or a patient who refuses surgery or for whom surgery may have high functional or cosmetic risk. Dermatologists should be aware of evaluating relapses with videodermoscopy in patients treated with ^{188}Re brachytherapy because arborizing-like vessels could be due to fibrotic reaction and neo-angiogenesis. The histological type of sdBCC must alert dermatologists to both the efficacy of brachytherapy and the time to free-from-recurrence.

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