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RESEARCH ARTICLE

MEDICAL PHYSICS

A novel tool for predicting the dose distribution of non-sealed ^{188}Re (Rhenium) resin in non-melanoma skin cancers (NMSC) patients

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Abstract

Background: High-dose rate brachytherapy using a non-sealed ^{188}Rhenium resin (^{188}Re) is a recently approved treatment option for non-melanoma skin cancer (NMSC). The treatment goal is to deliver a personalized absorbed dose to the deepest point of neoplastic infiltration corresponding to the minimal target dose. The treatment consists of the application of a ^{188}Re-based resin over a plastic foil placed on the target skin surface. However, there is no treatment planning tool to assess the ^{188}Re activity needed for a personalized treatment.
Purpose: The paper aims to present a novel Monte Carlo (MC)-based tool for ^{188}Re-based resin activity and dose calculation, experimentally validated using Gafchromic EBT3 films.
Methods: MC simulations were carried out using FLUKA modeling density and composition of ^{188}Re resin. The MC-based look up table (LUT) was incorporated in an ad hoc developed tool. The proposed tool allows the personalized calculation of treatment parameters (i.e., activity to be dispensed, the treatment duration, and dose volume histograms), according to the target dimension. The proposed tool was compared using Bland–Altman analysis to the previous calculation approaches conducted using VARSKIN in a retrospective cohort of 76 patients. The tool was validated in ad hoc experimental set ups using a stack of calibrated Gafchromic EBT3 films covered by a plastic film and exposed using a homogenous activity distribution of ^{188}Re eluate and a heterogeneous activity distribution of ^{188}Re resin mimic the patient treatment.
Results: The agreement between the proposed tool and VARSKIN was evaluated on the investigated cohort with median range of target area, target depth, and treatment time equal to 4.8 [1.0–60.1] cm^2, 1.1 [0.2–3.0] mm, and 70 [21–285] min, with a median range of target dose (Gy) of 23.5 [10–54.9]. The calculated minimal target doses, ranged from 1% to 10% for intermediate target depths (1.2 ± 0.7 mm), while showing significant differences in the estimation of superficial (maximal) target doses. The agreement between MC calculation and measurements at different plans in a stack of Gafchromic EBT3 films was within 10% for both the homogenous and heterogeneous activity distribution of ^{188}Re. Worst agreements were observed for absorbed doses lower than 0.3 Gy.

Federico Zagni, Sara Vichi, and Giulia Paolani contributed equally to this work.

Conclusions: Our results support the implementation of our MC-based tool in the practical routine for calculating the ^{188}Re resin activity and treatment parameters necessary for obtaining the prescribed minimal target dose.

KEYWORDS
^{188}Re, dose estimation, Monte Carlo dosimetry, radio-chromic films, skin brachytherapy

1 | INTRODUCTION

Treatment with non-sealed ^{188}Rhenium (^{188}Re) resin (SCT Oncobeta, Munich, Germany) is a recently approved treatment option for non-melanoma skin cancer (NMSC). This technique, also indicated as high-dose rate brachytherapy,[1] relies on ^{188}Re, which is a beta emitting (2.2 MeV, 85% yield) radionuclide with a half-life of 16.9 h, an average and a maximum range in water of 3.8 and 11 mm, respectively. The 92% of its energy is deposited up to a depth of 3 mm from the surface of the skin lesion.[1]

The brachytherapy procedure relying on the use of ^{188}Re-based resin can be performed for all those patients who are not eligible for or refuse excisional surgery. The ^{188}Re-based resin, provided in an ad hoc carpoule, is applied using a dedicated brush shielded with tungsten.[2] To prevent undesired skin contamination, the resin is applied on a 7 μm foil placed over the skin lesion instead of directly on the patient skin. This approach has been shown to be highly effective, highly tolerable, and minimally invasive.[2–4]

From a dosimetric point of view, the standard approach reported in Refs 2, 3 is based on the use of VARSKIN. The VARSKIN software is a reference tool for skin contamination dosimetry assessments approved by the U.S. Nuclear Regulatory Commission.[5] It has been used extensively to calculate the dose to the skin resulting from contaminants in direct contact with skin or with protective clothing.[6] The code uses six pre-programmed source geometries, source volumes, and a wide range of user-selectable radionuclides.

However, several authors found the accuracy of VARSKIN not satisfactory,[7,8] in particular in the presence of air gap or covering material over the treated tissue.

Moreover, there is no treatment planning tool to assess the ^{188}Re resin dispensing activity or to predict the absorbed dose distribution in the target areas. Thus, we developed and tested an ad hoc Monte Carlo (MC)-based tool for personalizing the calculation of ^{188}Re activity to be applied on the lesions of patients with NMSC. Our tool allows the calculation of the activity applied on the foil placed over the skin lesion to guarantee an acceptable dose to the target tissue taking into consideration the lesion area and depth as well as the characteristics of ^{188}Re.

The paper aims to present a novel MC-based approach for dose calculation, compared to VARSKIN software and validated with experimental measurements using Gafchromic EBT3 films.

2 | MATERIAL AND METHODS

2.1 | Monte Carlo simulations

MC simulations were carried out using FLUKA,[5] a general MC code for modeling particle transport and interaction with matter.

Although this MC code was initially developed for high-energy physics experiments, its range of application has been gradually extended to lower energies making it suitable also for the medical field. The code is now well-validated for applications in this field, particularly for modeling electromagnetic (EM) interactions. Its validation has been demonstrated by an increasing number of publications, covering the production of medical radioisotopes,[6] as well as proton and ion therapy applications,[7,8] radiation safety design,[9] and radiation detector modeling and optimization.[10,11]

In the current work, we used FLUKA v2011.2x.5 in combination with the graphical interface Flair 2.3. Regarding the physical processes, radioactive decay was activated to model the decay scheme of ^{188}Re, including the characteristic beta emission spectrum, and emitted x-ray and gamma ray photons, such as Compton scattering, photoelectric absorption, electron scattering, ionization, and bremsstrahlung radiation. Photons and electrons with energies of 5 keV or lower were modeled to be absorbed locally with no further transport.

All the simulation parameters are summarized in Table 1 following the AAPM TG 268[13] recommendation and further described in the following subsections.

2.1.1 | Monte Carlo simulations in patient-like geometry

A specific MC simulation was carried out considering the real conditions of treatment delivery in patients. In particular, as the resin formulation is patented and the detailed composition has not been released by the manufacturer, based on the information from the company,

TABLE 1 MC simulation parameters following the AAPM TG 268[13] recommendation.

Checklist item #	Item name	Description	References
2, 3	Code, version/release date	FLUKA v2011.2x.5 in combination with Flair 2.3	5
4,17	Validation	FLUKA has been validated for lower energies making it suitable also for the medical field.	6–11
5	Timing	N/A	N/A
8	Source description	The source has been modeled as a homogenous 0.1 mm-thick cylinder of epoxy ($H_{19}C_{18}O_3$) within an air world. The plastic foil was simulated as PMMA ($H_8C_5O_2$) with density 0.95 g/cm^3 while the petri was simulated as Plexiglass ($H_8C_5O_2$) with density 1.17 g/cm^3. Finally, the skin was simulated based on the NIST database of materials and compound, which are in turn based on ICRU and ICRP tissue compositions.	5,12
9	Cross-sections	FLUKA Default Library for EM interactions (i.e., EM-CASCAde package.	14
10	Transport parameters	FLUKA Default Parameters with exception of the Energy threshold (set to 5 keV for both transport and production of secondary particles	14
11	VRT and/or AEIT	None used. Full analogue Monte Carlo was performed.	N/A
12	Scored quantities	The scored quantity was energy per gram per primary expressed in GeV/(g*primary, converted in dose per unit of activity and time expressed in Gy/(MBq·min), following the steps reported in the main text.	5
13, 18	# histories/statistical uncertainty	The number of simulated primaries was set to 10^7 in order to get an uncertainty on the scored quantities lower than 1%.	N/A
14	Statistical methods	The statistical uncertainty of each scored quantity is calculated by FLUKA as standard deviation of the results recorded for all simulated cycles, being the cycles identical runs of the simulation with different starting seed.	5
15, 16	Postprocessing	The chosen output option was the USRBIN card of FLUKA (fully described in the main text). Conversion to Gy per unit of activity and time is described in the manuscript. No further postprocessing was necessary.	5

the resin was modeled as epoxy ($H_{19}C_{18}O_3$), with density 1.2 g/cm^3, with an estimated thickness of 0.1 mm, over a 7 μm plastic foil (simulated as PMMA H8C5O2, with density 0.95 g/cm^3) between the resin and the target area. The source has been modeled as a homogenous 0.1 mm-thick cylinder of epoxy within an air world, varying its radius to match the typical target area (minimum simulated area 1 cm^2, maximum simulated area 40 cm^2, according to the smallest and largest target areas encountered in the clinical experience). We calculated the in-depth absorbed dose from 10^{-5} mm to 5.0 mm along the axis of cylinder with non-uniform sampling frequency, higher close to the skin surface for each simulated area (a total of 45 simulations, from 1 to 5 cm^2 with 1 cm^2 step, from 5.5 to 20 cm^2 with 0.5 cm^2 step, from 21 to 25 cm^2 with 1 cm^2 step, and from 27.5 to 35 cm^2 with 2.5 cm^2 step and 40 cm^2).

2.1.2 | Monte Carlo simulations for phantoms

We performed additionally MC simulations to replicate two experimental situations.

The schematic representation of the MC geometry simulation for Gafchromic films is reported in Figure 1(a). The investigated geometries included (a) a homogenous solution of ^{188}Re eluate placed within a plastic 5-cm-diameter Petri (simulated as Plexiglass, $H_8C_5O_2$, with density 1.17 g/cm^3), having a thickness of 0.3 cm, in order to contain the liquid eluate, directly located on the top of four stacked Gafchromic films and glued with silicon (see Figure 1b) and (b) a ^{188}Re resin deposited over a 7-μm foil placed on the top of five stacked Gafchromic films (see Figure 1c).

The eluate was simulated as a water solution, as the actual percentage of the perrhenate ($^{188}ReO_4$) molecule mass relative to whole phantom was $5{\cdot}10^{-8}$ %.

The chemical composition, density, and dimensions of the Gafchromic layers,[17] as well as for the plastic 5-cm-diameter petri and the plastic foil, were also included in the MC simulation. The output dose was recorded in the central 28-μm active layer of the simulated film.

2.1.3 | Dose scoring

Considering absorbed dose assessment, it must be notice that FLUKA scores the dose in unit of GeV/(g*primary), so a suitable conversion factor was needed for converting the total dose deposited per number of particle into Gy/(MBq*min),

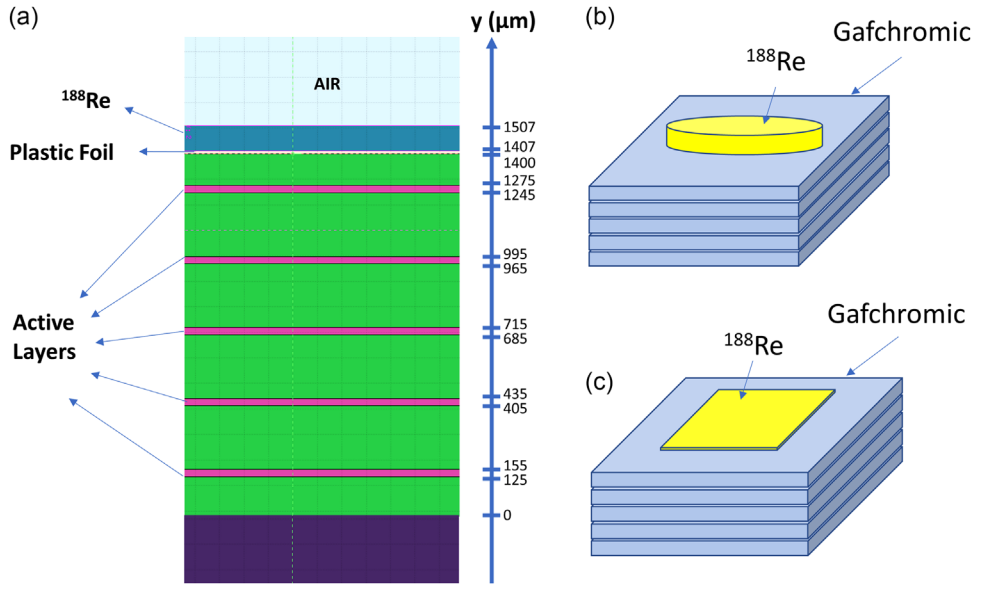

FIGURE 1 Schematic representation of (a) Monte Carlo (MC) geometry simulation for Gafchromic film, (b) homogenous, and (c) heterogeneous phantoms experimental set-up.

for example, assuming 1 GeV/g = $1.6{\cdot}10^{-10}$ J/g = $1.6{\cdot}10^{-7}$ J/kg = $1.6{\cdot}10^{-7}$ Gy and 1 primary = 1 Bq·s, so 1 MBq·min = $60{\cdot}10^{6}$ Bq·s. Thus 1 GeV/(g·primary) = 1 GeV/(g·Bq·s) = $1.6{\cdot}10^{-7}{\cdot}60{\cdot}10^{6}$ Gy/(MBq·min) = 9.6 Gy/(MBq·min). The dose per unit activity and time was multiplied by the total treatment activity and treatment time to calculate the absorbed dose, similarly to the approach implemented within VARSKIN.

The chosen output option consists in a large voxelized 3D map of the dose (USRBIN card of FLUKA) from which it was possible to select a volume under the radioactive source (area equal to the simulated source and thickness of 5 mm with 20 μm slices). A look up table (LUT) was finally created reporting the dose (per unit of activity and time) as a function of depth and simulated area.

The statistical uncertainty was calculated by FLUKA as standard deviation of the results recorded for all simulated cycles (where cycles are identical runs of the simulation with different starting seed).

In addition, The FLUKA package makes use of the NIST database of materials and compound,[12] which are in turn based on ICRU and ICRP tissue compositions. For the purpose of this work, the tissue-equivalent material, as representative of the clinical target volume, was used for the dose scoring.

According to,[15] all photon and beta spectrum used in FLUKA are taken from the NuDat database, which is part of the NNDC database.[16] Uncertainties in dose rate and air-kerma rate calculations originate from uncertainties affecting energy and intensity values.

2.2 | Comparison between the MC-based and VARSKIN LUT

The MC-based LUT was compared with that obtained using VARSKIN software,[17] reported in literature as a reference tool for brachytherapy using ^{188}Re resin.[2,4] VARSKIN allows the calculation of the dose at a specified depth, assuming a homogenous activity distribution in several reference geometries. We run VARSKIN version 5.2[18] for each combination of target area and depth to obtain a LUT with the same sampling as the MC-based one, in order to obtain a point-by-point dosimetric comparison.

2.3 | MATLAB GUI tool

We developed a calculation tool using the MATLAB (MathWorks, Natick, USA) version R2021b. The tool is based on the pre-calculated MC lookup tables (LUTs), reporting the absorbed dose/(MBq*min) at different depths due to the uniform displacement of ^{188}Re-based resin on different target areas, obtained from the MC simulations. Given the total dispensed activity, the lesion area, and the reference depth the tool calculates the treatment time necessary to achieve the prescribed dosage, also providing the mean and maximal doses, and dose-volume histogram (DVH) of the target lesion.

The workflow of the tool, through the GUI showed in Figure 2(b), is detailed as follows. The GUI allows the selection of MC-based pre-calculated LUT, already converted from .csv format to MATLAB (.mat) object, using the button “LOAD”. The loaded LUT reported different

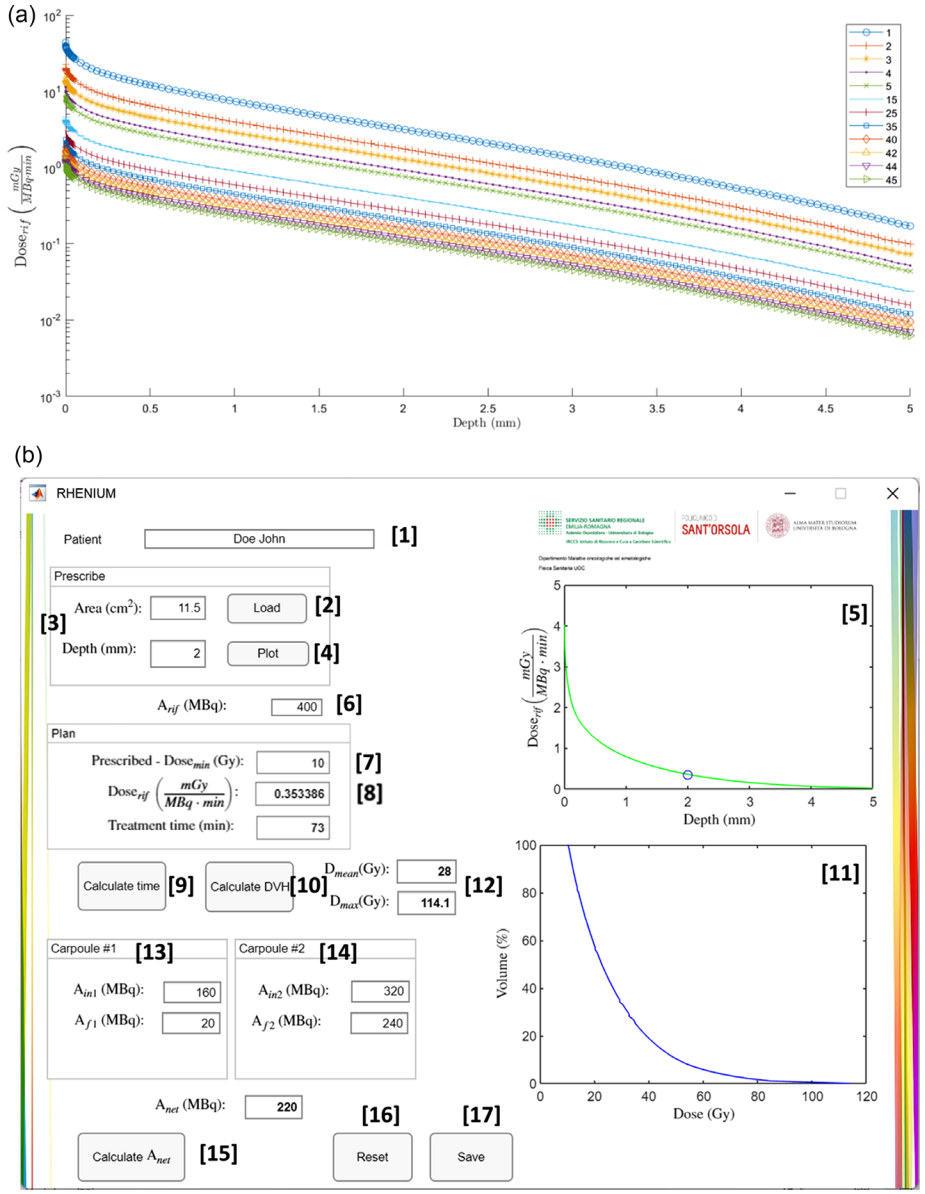

FIGURE 2 (a) Several examples of MC-calculated mGy/(MBq*min) versus the lesion depth according to twelve different target areas (i.e., 1, 2, 3, 4, 5, 15, 25, 35, 40, 42, 44, 45 cm^2), indicated with different combinations of lines and symbols. (b) The developed MATLAB GUI. After entering the patient's name and surname [1], the GUI allows the loading of the LUT table by using the button "Load" [2]. The user must insert the treatment area and reference target depth [3] previously obtained in the patient preparation phase, as described by Castellucci et al. [3] Then, by pushing the button "Plot" [4], the GUI shows the mGy/(MBq*min) trend as a function of the treatment depth along the central axis of the chosen area with a green line, as well as the mGy/(MBq*min) at the selected depth with a blue circle [5]. After the user specifies the activity included in the carpoule [6] and the personalized prescription [7], by pushing the button "Calculate time" [8] the GUI shows in bold numbers the mGy/(MBq*min) value and the suggested treatment time [9]. Moreover, thanks to the button "Calculate DVH" [10], the GUI shows the DVH as a blue line [11] as well as the mean and maximum dose [12]. The DVH is automatically saved as a. mat object with the patient's name and surname. Then, the initial and final activity from one or two carpoules can be inserted in the boxes [13] and [14]. Subsequently, the button "Calculate A_{net}" shows the residual activity which can be added to the initial one (A_{rif}) to reduce the treatment time and update the DVH. Finally, the button "Reset" [15] resets the GUI and the button "Save" [16] saves the patient-related parameters, the DVH and the mean dose. DVH, dose-volume histogram; LUT, look up table; MC, Monte Carlo.

mGy/(MBq*min) curves at increasing depths according to different simulated target areas: representative examples are shown in Figure 2(a).

The tool allows to insert patient and target specifications (i.e., patient name, target area, and reference target depth) and directly loads and shows the distribution corresponding to the specified target area (green curve in Figure 2b[5]) and the value of the dose per unit of activity and time at the reference target depth (i.e., $Dose_{ref}$, represented as a blue point in Figure 2b[5]), specified in

the "Dose$_{ref}$ ($\frac{mGy}{MBq \cdot min}$)" field (Figure 2b[8]) and uniquely identified by target area and depth.

In addition, the total activity used to cover all the target surface is obtained by using the button "calculate the A_{net}" using the following formula:

$$A_{net} = \sum_{j=1}^{n} A_{in,j} - A_{f,j}$$

where $A_{in,j}$ and $A_{f,j}$ are the initial and the residual activity inside the j-th carpoule, respectively. $A_{in,j}$ and $A_{f,j}$ are obtained by measuring the carpoule activities before and after the resin deposition with the activity calibrator supplied by the manufacturer.

Based on Dose$_{ref}$, and total dispensed activity, the tool calculates the treatment time ("calculation time" button) necessary to achieve the prescribed dose at highest target depth defined by the user into the proper field (i.e., "Prescribed Dose$_{min}$ (Gy)" Figure 2b[7]), represents the minimal dose to the target using the formula:

$$T_0\,(\text{min}) = \frac{\text{Prescribed Dose}_{\text{min}}}{A_{net} \cdot \text{Dose}_{rif}}$$

However, the above calculated T_0 did not consider the decay of ^{188}Re during treatment. To take into account the physical decay, the treatment time need to be prolonged according to a corrected factor (*CF*) determined as follows:

$$CF = \frac{\lambda T_0}{1 - e^{-\lambda T_0}}$$

where λ is the physical decay constant for ^{188}Re and T_0 is the exposure time irrespective of the activity decay during treatment. Thus, the corrected exposure treatment time (T_{tmt}) becomes:

$$T_{tmt}\ (\text{min}) = \frac{\text{Prescribed Dose}_{\text{min}}}{A_{net} \cdot \text{Dose}_{rif}} \cdot CF$$

Finally, the button "Calculate DVH" calculates and shows the dose-volume histogram of the treated target, considering the depth dose distribution obtained from the MC simulations. In addition, the mean and the maximal doses in Gy are calculated and reported in Figure 2(b).[12]

2.4 | Validation phantoms

Two types of phantoms were built for comparing results between proposed calculation methods (Figure 1b-c) as reported in Material and Methods subsection "Monte Carlo simulation".

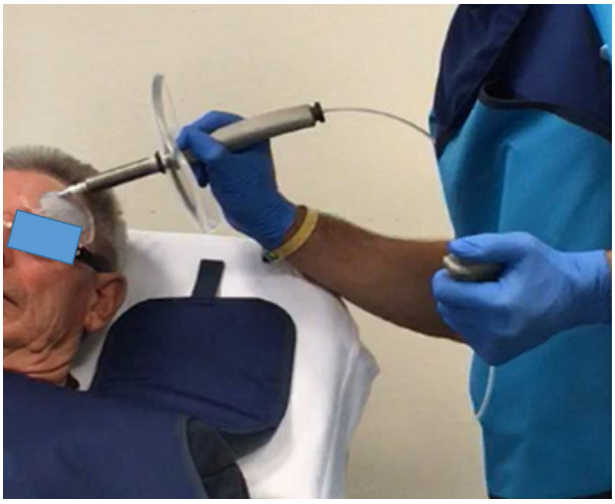

FIGURE 3 A representative example of treatment set-up. The resin is applied by using the dedicated shielded brush on the 7-μm plastic foil, located on patient skin. The target is contoured directly on the plastic foil by an expert dermatologist, with a safe margin of 3 mm. The entire clinical workflow is described in Castellucci et al.[3]

The first was prepared using a liquid solution of ^{188}Re, obtained directly from the ^{188} W/^{188}Re generator's elution to produce a homogeneous activity distribution. The solution was injected with a syringe inside a 5-cm-diameter plastic ring (with a thickness of 0.3 cm), directly located on the top of five stacked Gafchromic films. To obtain a wide dose range (about 0.1–4 Gy), in four of five Gafchromic films, an activity of 86 MBq was placed on the upper Gafchromic film for 4, 10, 25, and 55 min.

The second phantom was prepared with the ^{188}Re resin and deposited as for the patient treatment plan, that is, the radioactive resin was applied over a 7-μm foil placed on the upper Gafchromic film to evaluate the level of dose uniformity. Several Gafchromic stacks were irradiated using a 4 cm^2 squared surface area, 206 MBq and for 2, 3, 6, 15 min, obtaining a dose range of about 0.7–11 Gy). Schematic illustrations of the described phantom are reported in Figure 3(c)-(d) for the eluate and resin experiment, respectively.

2.5 | Gafchromic calibration

The film used for this work was the third generation of the Gafchromic film, model EBT3 (Ashland, Inc., Wayne, NJ).

The calibration of Gafchromic films was performed according to[19] using a linac Versa HD (Elekta AB, Stockholm, Sweden). Twelve Gafchromic films were exposed to increasing values of monitor units (from 10 to 2000 monitor units) corresponding to increasing dose values (from 7.49 to 1742.90 cGy). The films were digitalized on an EPSON Expression 10000 XL flatbed document scanner (Epson America, Long Beach, CA). All films

were scanned using the same scanner orientation and position (i.e., at the center of the scanning surface). The storage, handling processes, and film analysis method adopted in this work were based on.[19] The irradiation time for the phantom studies was selected to deliver a nominal dose lower than 12 Gy at the Gafchromic film.

To assess the uniformity of the resin deposition and the absorbed depth dose, the films used in this work were cut into (5 × 5) cm^2 pieces from the same batch (Lot No. 11021501).

The net optical density (NOD) was calculated with the following equation:

$$\mathrm{NOD} = \mathrm{ODC} - \mathrm{ODB} = -\left(\log_{10}(PC) - \log_{10}(PB)\right)$$

where ODC is the optical density after irradiation (calibration) and ODB is the background optical density.

All the acquisitions were imported in an ad hoc MATLAB tool, and a calibration curve (dose in Gy vs. NOD) was obtained with the following formula:

$$\mathrm{Dose\ (Gy)} = (a - c * 10^{-\mathrm{NOD}})/(10^{-\mathrm{NOD}} - b)$$

for the red, green, and blue channels of the film acquisition scanner. Only the red channel was for subsequent dose evaluations on Gafchromic films, considering that the investigated dose range is up to 10 Gy.

2.6 | Data analysis

The MC results for the depth absorbed dose distribution at the sensitive layer position of Gafchromic films were compared to experimental measures.

The mean value on a region of interest placed on the irradiated area of each Gafchromic films was converted into dose (D_m) through the calibration curve. The difference between the dose distribution obtained by Gafchromic film (D_m) and calculated using the Monte Carlo code (D_{MC}) was determined according to the following equation:

$$\Delta D = \frac{D_m - D_{MC}}{D_{MC}}$$

We used a similar equation to compare the dose estimated by the MC code for each area and depth representing the target lesion and the one obtained using the VARSKIN version 6 code. The standard deviation of the absorbed dose determined using the Gafchromic film, σ_m,was calculated on a central ROI of approximately 1 × 1 cm^2 as:

$$\sigma_m = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(x_i - \bar{x})^2}$$

where x_i is the measured dose at i-th pixel, $\bar{x}$ is the average value across the exposed area within each Gafchromic EBT3 film. The σ_m value was used to assess the surface heterogeneity due to the application of radioactive resin on the upper foil.

In addition, Bland–Altman analysis was used to compare the MC results with Gafchromic measurements for the resin and eluate experiments and to compare patient doses estimated with MC simulations and VARSKIN.

2.7 | Uncertainty assessment

The uncertainty on the reported results was assessed as follows. As previously specified, the MC calculation was set with a proper number of primaries in order to obtain an associated uncertainty lower than 1%. The uncertainties on the fit parameters of the calibration curve were provided by the MATLAB "fit" function. The overall uncertainty on the measured absorbed dose with the Gafchromic measurements was obtained through the propagation of the uncertainties. The estimated relative error was lower than 5% and 3% for doses higher that 1 and 10 Gy, respectively.

2.8 | Patients cohort

The patient's cohort included consecutive NMSC patients treated at the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) University Hospital of Bologna, Italy. All patients followed the standard clinical workflow as described in Castellucci et al.[2] This consists of mixing the Rhenium-188, in the form of insoluble dirhenium-heptasulfide microparticles, with a specially designed acrylic resin matrix: the final compound, ready for therapy, is contained in a single-use sealed and calibrated carpoule. This is operated with a specially designed shielded ergonomic applicator holding the carpoule containing the radioactive compound.[2] The tool for resin application is designed to apply the radioactive matrix with a brush shielded with tungsten.[2] The dedicated shielded brush enables the radioactive resin application on an adhesive 7 μm plastic foil placed over the skin lesion to avoid the contamination of the patient's skin.[3] The carpoule activity is measured before and after the resin application using an ad hoc activity calibrator (Comecer, Bologna Italy) provided by Oncobeta. A representative picture of resin deposition on patient is shown in Figure 3.

The target area and depth and the administrated activity were used to calculate the irradiation time and to provide appropriate dosimetric evaluation. Immediately after the treatment, the plastic foil was removed, and a contamination control was performed before patient discharge.

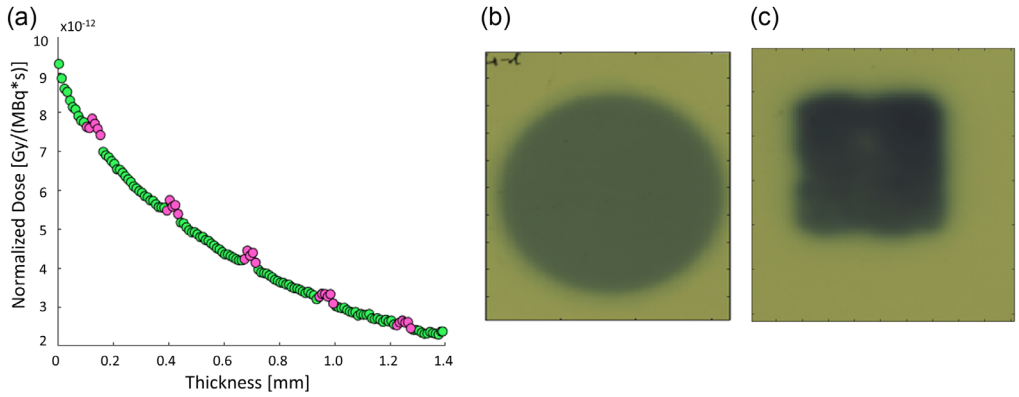

FIGURE 4 (a) Normalized absorbed dose versus target depth. In purple, dose values corresponding to Gafchromic active layer are emphasized. Upper Gafchromic films of (b) homogenous and (c) heterogeneous ^{188}Re phantom obtained using the ^{188}Re eluate and resin.

Dosimetric calculations were performed both with VARSKIN and the developed MATLAB tool to compare and assess the agreement between the two methods.

For local control, patients were classified according to Dermoscopy (DermLite 3 Gen, San Juan Capistrano, California, USA) and digital non-polarized contact Dermoscopy (Foto Finder dermatoscope, Teachscreen Software, Bad Birnbach, Germany) and, if clinically needed, a biopsy. Adverse events were assessed by experienced clinicians according to Common Terminology Criteria for Adverse Events (CTCAE 5.0).[20]

3 | RESULTS

3.1 | Monte Carlo simulations

Figure 1(a) shows the geometry modeled for the MC simulation associated with the resin experiment, as illustrative example. A similar approach was adopted to simulate the eluate geometry. The MC geometry involves the ^{188}Re layer, plastic foil, and Gafchromic internal composition. The absorbed dose, normalized per deposited activity and treatment time, is largely dependent on the considered Gafchromic active layer as shown in Figure 4(a). Example of acquired Gafchromic films are reported for eluate and resin in Figure 4(b)-(c), respectively.

3.2 | Monte Carlo and VARSKIN comparison

Table 2 shows the differences of absorbed dose using VARSKIN and MC code according to the simulated treated area at various depths. In more detail, percentage differences were calculated for every combination of target area and depth. A percentage difference ≤5% was observed for depth values between 0.4 and 1.5 mm and all the investigated target areas while a percentage difference ≤2% was observed for a subset of the investigated target depths and areas (Table 2).

Higher discrepancies (≥10%) were found between the two methods considering superficial doses (for depth less than 0.05 mm), leading to discrepancies in the calculated maximum doses and in the prescribed activity (which depend on the maximal depth) for target depth higher than 3 cm. The differences between the estimated target doses calculated using FLUKA and VARSKIN and the ^{188}Re treatment activities adopted in our patient cohort are reported in the subsection "Cohort of patients."

3.3 | Gafchromic calibration

The calibration curves obtained with the multi-channel approach are reported in Figure S1 of the Supplementary material.

3.4 | Gafchromic measurements

Figure 5(a)-(b) show the plots obtained from the Bland–Altman analysis performed to compare the doses calculated by MC simulation and the those obtained using the Gafchromic films for all the film layers applied in the investigated set-up. A total of 14 and 16 dose comparisons are reported for the eluate and the resin phantom setup, respectively. Two films for the eluate phantom were discarded due to contamination.

In particular, both for eluate (Figure 5a) and resin (Figure 5b) experiments the difference between the absorbed dose obtained with the Gafchromic film and the MC simulation is plotted against their mean. The 95% Confidence Interval (CI)is also shown.

An agreement within 10% was observed between the investigated methodologies for doses commonly used in clinical practice (greater than 0.5 Gy), with a maximum dose difference of 0.3 Gy. Significant discrepancies

TABLE 2 Percentage difference between MC simulation and VARSKIN in every simulated combination of target area and depth.

	Target area (cm^2)										
	1	**2**	**3**	**4**	**5**	**10**	**15**	**20**	**25**	**30**	**35**
0.005	27%	26%	25%	24%	25%	24%	24%	24%	23%	24%	24%
0.01	23%	22%	21%	20%	21%	21%	20%	20%	20%	20%	21%
0.025	17%	16%	15%	14%	15%	15%	14%	14%	14%	14%	14%
0.05	12%	11%	10%	9%	10%	11%	10%	10%	9%	10%	10%
0.1	8%	7%	6%	5%	6%	7%	6%	6%	5%	6%	6%
0.125	7%	6%	5%	4%	5%	6%	5%	5%	4%	5%	6%
0.15	6%	5%	5%	4%	5%	5%	4%	5%	4%	5%	5%
0.175	6%	5%	4%	3%	5%	6%	4%	5%	3%	5%	5%
0.2	6%	5%	4%	4%	5%	6%	4%	4%	3%	5%	5%
0.3	5%	4%	3%	2%	4%	6%	4%	4%	3%	4%	4%
0.4	3%	2%	2%	1%	3%	5%	3%	3%	2%	3%	3%
0.5	2%	2%	1%	1%	2%	4%	3%	2%	1%	2%	3%
0.6	1%	1%	1%	0%	2%	4%	2%	2%	1%	2%	2%
0.7	1%	0%	0%	0%	1%	4%	2%	2%	1%	2%	2%
0.8	0%	0%	1%	1%	1%	3%	2%	2%	0%	1%	2%
0.9	0%	1%	1%	2%	0%	3%	1%	1%	0%	1%	2%
1	1%	1%	1%	2%	1%	3%	0%	1%	0%	1%	1%
1.5	4%	3%	4%	4%	3%	1%	1%	1%	2%	1%	0%
2	6%	6%	6%	6%	5%	1%	4%	4%	5%	3%	2%
2.5	8%	8%	8%	8%	6%	4%	6%	6%	7%	5%	4%
3	13%	12%	13%	13%	11%	9%	10%	10%	11%	9%	9%
4	22%	22%	22%	22%	19%	17%	18%	19%	19%	19%	18%
5	35%	32%	33%	34%	31%	27%	29%	28%	30%	28%	28%

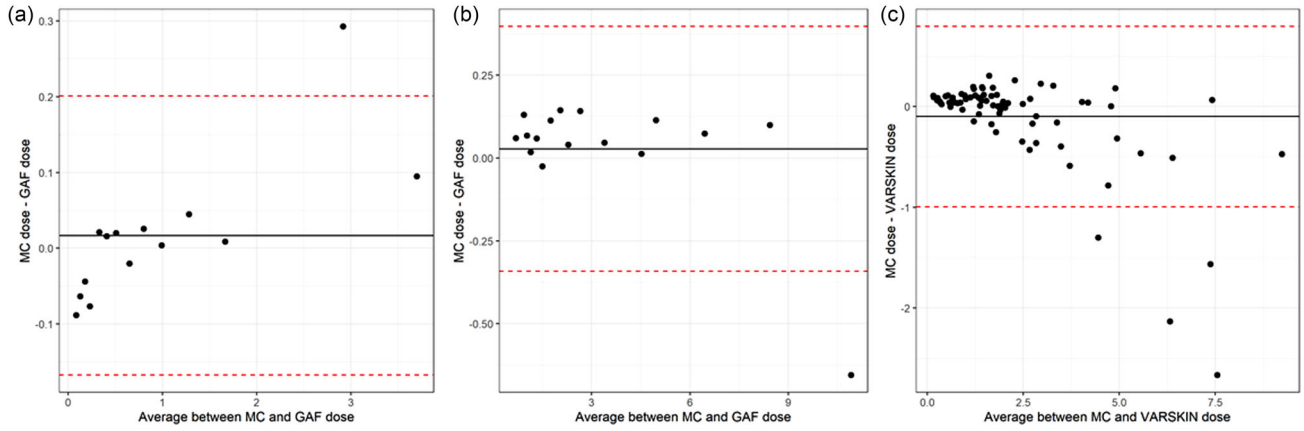

FIGURE 5 Bland–Altman plot comparing doses calculation using MC simulations versus Gafchromic absorbed dose in (a) eluate-based experiment, (b) in resin-based experiments. (c) Bland–Altman plot of absorbed doses calculated using the proposed tool versus VARSKIN in the investigated cohort of patients. Red lines represent 10% of discrepancies.

(higher that 25%) are registered for doses lower than 0.3 Gy, as highlighted by the eluate experiment.

No significant biases (<0.02 Gy) were found between Gafchromic and MC based absorbed doses. A single relevant outlier was found for the highest dose point with the resin setup considering absolute dose values, although the percentage difference was still below 10%. The standard deviation σ_m of measured dose using Gafchromic decreased with the increase of absorbed dose with a median value of 6% for eluate, while showed values around 16% for resin due to heterogeneity in resin deposition.

TABLE 3 Summary of NMSC patients' and targets' characteristics.

	N° [%]	Median [Range]
Age (year)		82 [51; 97]
Sex (M/F)	59 [63%]/35 [37%]	
Histology		
BCC	57 [60.6%]	
SCC	37 [39.4%]	
Target depth (mm)		1.1 [0.2—3.0]
Target area (cm^2)		4.8 [1.0–60.1]
GTV volume (cm^3)		0.45 [0.05–15.0]
Administered activity (MBq)		213 [36–1300]
Treatment time (min)		70 [21–285]
Target dose (Gy)[b]		23.5 [10–54.9]
Maximum dose (Gy)[a]		156.0 [27.3–400.0]
Ratio between maximum and target dose		5.5 [2.0–32.1]
Dose (Gy) to 0.5 mm depth		46.9 [9.43–159.4]
Mean dose (Gy)		48.3 [17.7–126.1]

[a]Dose at 0.0001 mm depth.
[b]Dose to the deepest point of neoplastic invasion.

3.5 | Cohort of patients

Seventy-five consecutive patients, from September 2017 to May 2021, were included in this study, for a total amount of 94 treated lesions (16 patients with multiple targets) located on scalp (19%), face except nose (29%), nose (22%), ears (10%), and body (20%). The main characteristics of patients and tumors are reported in Table 3. The reported absorbed dose values and the ratio between maximum and target doses were originally calculated with VARSKIN as they were included in the clinical patient report. Our study revealed percentage differences on prescribed activity using VARSKIN and our MC-based tool ≤2% and ≤5% only in the 38% and 64% of the investigated cohort of patients, respectively.

The Bland–Altman plot used to compare the dose at target depth calculated with MC and VARSKIN is shown in Figure 5(c). The 95% CI ranged from −8.99 Gy to 9.78 Gy with a systematic bias of 0.40 Gy.

In particular, the median target dose calculated with VARSKIN was 1.84 Gy ranging from 0.2 to 9.0 Gy while the median target dose calculated with the proposed approach was 1.83 Gy ranging from 0.1 to 9.4 Gy.

4 | DISCUSSION

The ^{188}Re delivers a highly selective surface beta radiotherapy to the tumor region. The high energy (> 1MeV) electrons from this beta emitter isotope are therapeutically effective only at a short distance, allowing sparing underlying healthy tissue better than using gamma photon radiotherapy or classic brachytherapy.[4]

Beta radiation deposits more than 90% of the dose in the first 2 mm of the skin, which is the depth usually involved in superficial tumor invasion.[4] In this work, a novel dosimetric method was described. The proposed approach was compared with the well-established VARSKIN procedure and validated using Gafchromic EBT3 films. In addition, it has been used in clinical practice since 2019 as it is faster and more suitable for typical clinical requirements, as VARSKIN is un-directly and iteratively used by modifying the total exposure time until the achieving of the treatment goal. On the contrary, the proposed tool allowed to directly estimate the total treatment time necessary to prescribed dose to the deepest point of neoplastic infiltration.

4.1 | Monte Carlo simulations

To assess the potential differences related to other MC approaches, we calculated the skin dose for ^{188}Re considering its spectrum and interpolating the data reported in Table 3 of Appendix of the recently published paper.[21] Limited to this experimental set-up, the percentage relative differences on calculated skin contamination dose using MCNP and GEANT4 resulted in 0.55% and 0.48% higher than the one calculated using FLUKA, respectively.

Other authors observed and reported that the dose calculated on the skin surface using VARSKIN is within 10% of other deterministic and probabilistic methods for point-like and planar sources.[18,22] Discrepancies with other methods appear when VARSKIN is used to model the presence of air-gaps or cover material (e.g., protective clothing). Compared to the EGS4 results,[23] VARSKIN underestimates the absorbed dose by nearly a factor of two in scenarios using high energy beta sources. These discrepancies suggest that energy loss in air and/or cover material is not handled accurately in VARSKIN.[22] Similar results were reported comparing VARSKIN and MCNP5 values in the presence of air gaps between contaminated clothing and the skin. Moreover, since the VARSKIN software has been developed for radioprotection purposes focusing on mean values at given depths, it did not allow considering the heterogeneity related to the resin application.

In our study, differences of doses calculated with our MC-based tool and VARSKIN software were ≤5% for intermediate target depths (between 0.4 and 1.5 cm), while discrepancies up to 35% were registered for superficial and deepest ones (see Table 2). These discrepancies are likely related the presence of the plastic foil covering the skin surface and the resin chemical composition embedded the ^{188}Re, which are poorly.

4.2 | MATLAB GUI tool

Our tool allows assessing the dose distribution considering 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.

The GUI allows planning the activity needed to be administered for each patient, reducing the overall calculation time, and saving all the steps from the dose prescription, target dimensions, and activity measurement to the evaluation of the dosimetric parameters.

The not-decay corrected treatment time (T_0) was calculated considering the prescribed dose, the total dispensed activity, and the dose per unit of activity and time at the reference target depth arising from the MC simulation. Then T_0 was properly prolonged to determine the appropriate treatment time (T_{tmt}) to account for the activity decay over T_0. As an example, a T_0 of 70 min implies a 2.3% of additional time needed to deliver the prescribed dose at the reference point that corresponds to a $T_{tmt} =$ 71.68 min, rounded to 72 min.

4.3 | Gafchromic measurements

Our MC-based tool was validated using Gafchromic measurements both in homogenous and patient-like phantoms. Our tool is in good agreement with the Gafchromic measurement, applied extensively in external beam radiotherapy (EBRT) and HDR brachytherapy[24–26] for assessing the average dose and its variability on a given surface.

The agreement between calculated and measured average values was within 5% for homogenous sources (eluate), while resulted equal to 7% for the patient-like geometry using the ^{188}Re resin. The measured absorbed dose was associated to larger standard deviation in resin compared with the eluate phantom, likely due to the user's ability to release in a single step a uniform quantity of resin using the brush.

However, significant discrepancies were found for very low doses (less than 0.3 Gy). These discrepancies are likely due to the uncertainties on the measured absorbed doses using the Gafchromic films, potentially reducible using pre-irradiated ones. These findings agree with discrepancies reported in EBRT for low delivered doses.[27] The accuracy improvement on measured absorbed doses delivered with ^{188}Re source using pre-irradiated Gafchromic films will be addressed in a future study. Scanner non-uniform response and orientation effects were not considered as films were scanned at the center of the scanner bed, keeping a consistent orientation.[27]

Gafchromic allows us to assess a heterogeneity dose index, helpful for determining the maximal dose and the full DVH with error bars.

4.4 | Cohort of patients

The tool was applied on a patient cohort consisting of 94 lesions treated for NMSC. Dosimetric evaluations were performed using both VARSKIN and the MC-based tool and agreement of 10% was observed between the compared methodologies, assessed by the Bland–Altman analysis, for most of the patients. Outlier points in Figure 5(c) are related to large (area $>$ 16 cm^2) and superficial (depth $<$ 0.5 cm^2) targets, and are mainly due to the difficulty of VARSKIN in dose evaluation in presence of air gap or covering material over the treated tissue, particularly affecting in superficial dose estimation.[7,8] Regarding the maximal target depth, the treatment is intrinsically limited by the physical characteristics of ^{188}Re (maximum range in tissue 11 mm) that also lead to high inhomogeneities in the deposited dose at increasing depth. In our clinical experience the median [range] target depth was 1.1 [0.2–3.0] mm, thus the median [range] ratio between the maximum dose (to the skin) and the target prescribed dose was 5.5 [2.0–32.1]. In addition, considering the observed discrepancies between VARSKIN and the MC-based tool, a treatment personalization with dedicated dosimetric tools is recommended.

4.5 | Limitations

A possible limitation of our approach is the assumption of a uniform circular dose distribution across each 20-μm thick slabs determined using the MC-based depth dose profile. This simplification neglects the inhomogeneities in the absorbed dose deposition at the edges of the target, whose impact might be significant for non-circular target or small area regions. In addition, the source has been modelled as a homogenous 0.1 mm-thick cylinder, although the reported experimental measurements demonstrated a non-uniform resin deposition, expressed in terms of higher measured standard deviation σ_m with respect to the liquid eluate experimental setup. Another limitation is that in the current version of the software, we did not consider the actual time integrated activity from the Rhenium deposition on the plastic foil up to the treatment end. This issue is related to the approach followed by VARSKIN. In our retrospective cohort, this approach can lead to an overestimation of the actual delivered dose thus the needed correction will be incorporated in the next version of the tool.

Finally, in this study the correlation between the reported toxicities and the absorbed dose simulated with VARSKIN and the MC-based tool was not addressed, and further investigations are needed.

5 | CONCLUSIONS

The current study demonstrates that our tool allows for the calculation of dosimetric features supporting the evaluation of the activity to be administered and predicting the radiation-induced effect after applying ^{188}Re-based resin on the lesion surface. Together with clinical information on target area and thickness, these data could be useful to personalize the treatment with this novel approved device and guide future research on dose-effect models.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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