Clinical and Translational Radiation Oncology 53 (2025) 100991

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

# Head and neck and skin (HNS) GEC-ESTRO and BRAPHYQS working groups joint critical review of the use of Rhenium-188 in dermato-oncology

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## ARTICLE INFO

*Keywords:*
Rhenium-188
Dermato-oncology
Non-melanoma skin cancer
Open-source radiotherapy
Dosimetry
Brachytherapy
Clinical outcomes
Multidisciplinary treatment

## ABSTRACT

Non-melanoma skin cancers are increasing globally, prompting the need for innovative, non-invasive treatment approaches. Radioactive rhenium ($^{188}$Re) paste has emerged as an open-source radiation-based modality in dermato-oncology, offering a novel alternative to conventional radiotherapy and brachytherapy. In this review, a systematic literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar for studies published over the past 20 years. Data were extracted from case series, pilot studies, and clinical trials, with particular emphasis on response rates, dosimetric parameters, and treatment-associated toxicity. Findings from approximately 240 patients demonstrated complete response rates ranging from 86 % to 100 % after one or two treatment applications, while dosimetric analyses revealed a rapid dose fall-off that effectively confines the therapeutic effect to a tissue depth of 2–3 mm, with most adverse effects being mild and transient. Notably, $^{188}$Re differs from conventional brachytherapy (specifically high-dose-rate modality) due to its open-source application and unique dosimetric profile. The use of $^{188}$Re in clinical practice mandates a highly specialized, multidisciplinary team, including radiation oncologists, nuclear medicine specialists, and experienced medical physicists, and strict quality assurance protocols, thereby limiting its application to carefully selected cases.

Although $^{188}$Re therapy offers a promising alternative for the treatment of superficial skin cancers, its distinct clinical and dosimetric characteristics warrant further randomized studies with extended follow-up to validate its efficacy and refine patient selection criteria under rigorous multidisciplinary oversight.

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https://doi.org/10.1016/j.ctro.2025.100991
Received 16 March 2025; Received in revised form 13 May 2025; Accepted 4 June 2025
Available online 8 June 2025

## Introduction

The World Health Organization (WHO) estimates that between 2 and 3 million cases of non-melanoma skin cancers occur globally each year, and this figure is likely an underestimation [1]. Its incidence is rising rapidly worldwide; This is mainly due to sun exposure and an aging population [2]. The majority of these skin cancers are diagnosed early and are low-risk, allowing successful treatment with surgery, medical therapies or radiation. Radiation has been used in treating skin cancers for over a century, with early reports describing direct radioactive radium applications onto the affected skin. Today, skin radiotherapy is delivered using external beam radiation or brachytherapy (BT, interventional radiotherapy) and has been successfully applied in non-melanoma skin cancers (such as basal squamous carcinoma (BCC) or cutaneous squamous cell carcinomas (cSCC), as well as in keloids and pre-cancerous skin conditions [3]. Non-surgical treatment options may be considered such as when excision could lead to significant cosmetic and/or functional loss, or in older and frail patients with increased surgical risk or in those who refuse surgery [4]. Other important factors influencing treatment selection include lesion location, number of concurrent lesions and size, immune status, treatment cost and convenience and patient preference. Consequently, with such a high and rapidly growing incidence of skin cancers worldwide, there is a need for the continued development of non-invasive, patient-centred treatment modalities that offer convenient and personalized care.

Recently, the radioactive compound Rhenium-188 ($^{188}$Re) has been introduced into dermato-oncology practice. Currently it is available in the form of a paste intended for direct skin application. Unlike traditionally used sealed isotopes in BT, $^{188}$Re is applied as an unsealed isotope. Other beta emitters have been proposed for the treatment of skin cancer and are at various stages of development, such as Yttrium-90 ($^{90}$Y) [5], Phosphorus-32 ($^{32}$P) [6], and Holmium-166 ($^{166}$Ho) [7].

So far, various terms have been used in literature in reference to $^{188}$Re treatments, such as “epidermal radiotherapy” and “epidermal radioisotope therapy”, “high-dose rate BT (HDR BT)”, “dermatological HDR BT” or “HDR beta-BT”.

Therefore, a dedicated joint task force of the GEC-ESTRO Head and Neck and Skin (HNS) and BRAPHYQS Working Groups was established to investigate the use of unsealed-source radioactive surface applications in skin radiotherapy. The use of $^{188}$Re in non-dermatological indications remains outside the scope of this paper.

## Aim and group membership

The aim of this paper is to provide a critical review of the evidence for the use of $^{188}$Re unsealed-source in skin radiotherapy (dermato-oncology). This review is not intended to provide set recommendations to healthcare systems regarding the choice of treatment for selected cases of non-melanoma skin cancer. This paper was authored by members of the GEC-ESTRO Working HNS Group and the BRAPHYQS Working Group, with contributions from a nuclear medicine expert (RB) and a young researcher (PAT). The joint project was approved by the GEC-ESTRO Committee. The final text was endorsed by ACT (Chair of BRAPHYQS WG), LT (Chair of GEC-ESTRO HNS WG) and FAS (Chair of the GEC-ESTRO Committee).

## Material and methods

A comprehensive literature review on superficial therapy treatments utilizing $^{188}$Re was established using specific and methodical search criteria. Keywords and phrases such as “Rhenium-188″, ”superficial therapy“, ”skin cancer treatment“, and ”beta emitter therapy“ were identified as central to our inquiry. We engaged academic databases and research platforms including PubMed, Scopus, Web of Science, and Google Scholar, given their extensive coverage of medical and scientific literature. The search was temporally bounded to include studies published within the last twenty years, aiming to capture the most recent advancements in this treatment domain. Furthermore, our search was refined to English-language articles or those translated into English, encompassing case studies, systematic reviews, *meta*-analyses, and clinical trials to ensure the relevance and quality of evidence. A particular focus was placed on studies assessing the efficacy, safety, dosing protocols, and long-term outcomes of $^{188}$Re therapy in comparison with alternative skin cancer treatments. This search strategy was designed to facilitate the identification of pertinent, high-quality literature on the application of $^{188}$Re in superficial therapy modalities, thereby underpinning our investigation with a solid foundation of contemporary scientific insights. A flow chart of the complete selection process is shown in Fig. 1.

### *$^{188}$Re: characteristics and properties*

Rhenium is a chemical element with atomic number 75. It is a transitional metal and belongs to group 7 of the periodic table [8]. Rhenium is regarded as one of the rarest elements found on the Earth. It is characterized by its dense, silver-grey metallic appearance. Rhenium has one stable isotope $^{185}$ Re and more than 30 unstable isotopes, including $^{188}$Re. It can be obtained by elution from a $^{188}$W/$^{188}$Re generator, or via neutron irradiation of tungsten oxide in a nuclear reactor to produce $^{188}$W, which subsequently decays to $^{188}$Re [9]. $^{188}$Re decays predominantly through the emission of high-energy beta particles (electrons) with mean energy of 763 keV and maximum energy of 2.12 MeV, along with a gamma emission of 155 keV which accounts for approximately 15 % of the overall radiation emission [9]. This specific radionuclide profile in combination with a relatively short half lifetime of 17 h makes $^{188}$Re a potent agent for medical applications in skin cancer. The strategic incorporation of $^{188}$Re in dermato-oncology stems from its unique beta emission profile. This energy spectrum ensures that the radiation dose is predominantly delivered to the surface and up to 3 mm deep. In conventional surface BT, the radiation dose it typical prescribed at a maximum depth of 5 mm below the skin surface [10]. $^{188}$Re is available for clinical applications under the brand name Rhenium-SCT®. Primary dosimetry standards for Re–188 are indeed available (e.g., from NIST) using methods like 4πβ–γ coincidence counting. These primary standards provide the basis for calibrating dose calibrators, ensuring accurate activity measurements in clinical practice [11,12].

### *Treatment with $^{188}$Re*

#### *Indications*

Rhenium-SCT® has been clinically used mainly for early and low risk BCC and cSCC [13–15]. Other indications cited in the literature include Bowen’s disease [16], extramammary Paget’s disease (EMPD) [17]or penile SCC [18].

#### *Application*

The procedure is performed in an outpatient setting without the need for anaesthesia and usually within a single visit. $^{188}$Re is applied using a specially designed applicator with a sealed radioactive compound. Next it is applied as an unsealed source directly to the skin surface. The application site is covered by a protective sterile and transparent foil to avoid the contamination of the patient’s skin. The radioactive paste, also called a resin, dries out during the treatment time and turns into a flexible film that is later removed with the foil. The duration of $^{188}$Re treatment, ranging from 30 min to up to 3 h, highlights the importance of personalized treatment protocols. The treatment time is calculated assuming that a dose of 50 Gy in the epidermis is sufficient to achieve complete tumor control [15]. Despite the fact that a target dose of 50 Gy to the epidermal layer is commonly adopted, Castellucci et al. [14] reported a clinical de-escalation protocol adjusting dose based on lesion characteristics. This tailored approach showed promising outcomes in terms of both tumor control and reduced acute toxicity, suggesting that

lower dose prescriptions may be effective for selected patients. These findings support the need for further research into personalized dose adaptation protocols. Although manual application of $^{188}$Re paste inevitably leads to variations in layer thickness, the short range of beta particles results in partial self-absorption, which may mitigate—but not fully correct—dose inhomogeneities. However, this assumption requires further validation. The heterogeneity introduced both by manual application and by the intrinsic consistency of the resin itself may lead to non-uniform surface dosing, especially in irregularly shaped lesions. Authors acknowledge that this aspect is underexplored in current literature and warrants systematic dosimetric investigation, potentially through phantom-based or Monte Carlo studies. Nonetheless, consistent application and careful dosimetry remain important to ensure uniform treatment.

The treated area involves the visible skin lesion extended with 3–5 mm margin beyond the visible peripheral boundaries of the lesion. This safety margin is intended to account for microscopic peripheral tumor spread. $^{188}$Re can penetrate the human tissue only up to 2 to 3 mm deep, therefore, it would be beneficial in relatively superficial skin cancers [14]. Safety peripheral and deep margins are crucial for treatment planning in order to encompass the entirety of the cancerous cells. High-frequency (>18 MHz) skin ultrasound is recommended to determine the required penetration depth [19].

*Treatment planning*

The use of software tools, such as VARSKIN 5.2 (United States Nuclear Regulatory Commission, USA) simulation software [20] enables accurate modeling of the dose distribution within the target tissue with uncertainties of less than 5 %. The software considers the specific characteristics of the $^{188}$Re source, including its initial activity and emission energy spectrum. The commercial version of OncoBeta® GmbH (Garching, Germany) is used under the trademark Rhenium-SCT® (Skin Cancer Therapy) which utilizes specially designed Excel spreadsheets intended for dosimetry calculation. The vendor specifies several constraints within the spreadsheet such as the area range from 0.5 cm$^2$ to 100 cm$^2$, the maximum depth of 3 mm and the activity per area value between 12 MBq/cm$^2$ and 200 MBq/cm$^2$. Other calculation programs have also been deployed for absorbed dose distribution of $^{188}$Re, such as Monte Carlo [21].

The treatment time is calculated based on the applied radioactivity and the required target depth in relation to the skin surface (Fig. 2).

In comparison to photons, the type of interactions of beta particles with matter are that their respective energy levels and application of bolus material to distance sealed sources from the skin lead to distinct depth dose profiles between $^{192}$Ir and $^{188}$Re in superficial applications [22]. The dose distribution curves for $^{188}$Re in skin cancer treatment demonstrate a rapid decrease in absorbed dose with depth, as characterized by a significant reduction in the dose with depth as shown in Fig. 3 [13,22].

At clinical distances (up to 3 mm below the skin surface), the absorbed dose due to the scattered photon component of 155 keV is negligible compared to the contribution from the beta emission. The dose-depth behavior of distinct radiation components, normalized to 50 Gy at 1 mm, can be analyzed to understand their differential contributions across various tissue depths, especially at depths beyond 3 mm. In clinical dosimetry and radiation protection, assessing dose deposition beyond this 3 mm threshold is crucial, as subtle variations in attenuation and energy distribution at these deeper layers can significantly influence patient safety, treatment effectiveness, and overall dosimetric accuracy. Furthermore, examining these data on both linear and logarithmic scales provides distinct perspectives: while a linear scale illustrates absolute dose changes, the logarithmic representation more clearly highlights subtle differences and variations otherwise obscured, thereby guiding more informed decision-making in dose optimization and radiation management (Fig. 4).

The full $^{188}$Re spectrum (red curve) encompasses contributions from

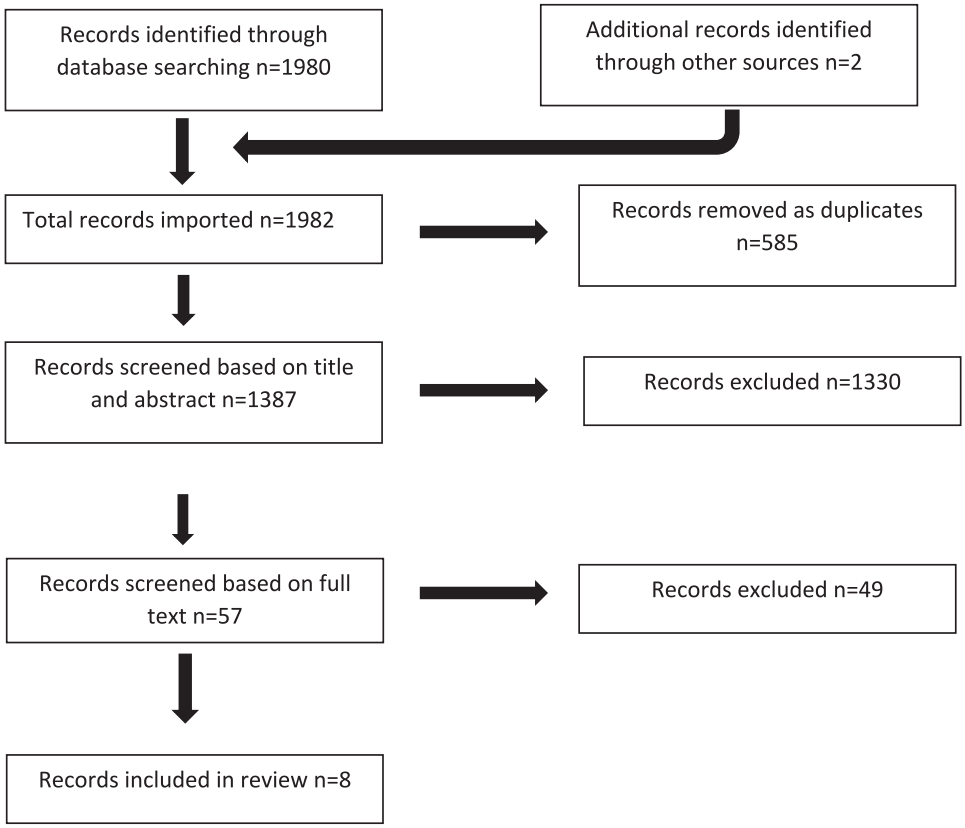


**Fig. 1.** Flow chart of the complete studies selection process.

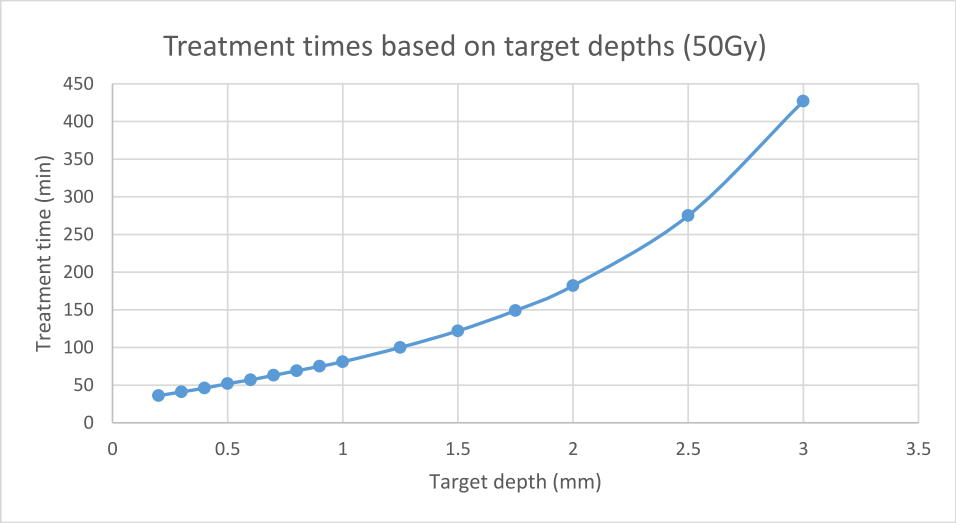


**Fig. 2.** Treatment times based on target depths (50 Gy). The values were calculated using a treatment area of 3 $cm^2$ and a standard activity of 72 $MBq/cm^2$ was used for the calculations. Based on the data provided by OncoBeta.

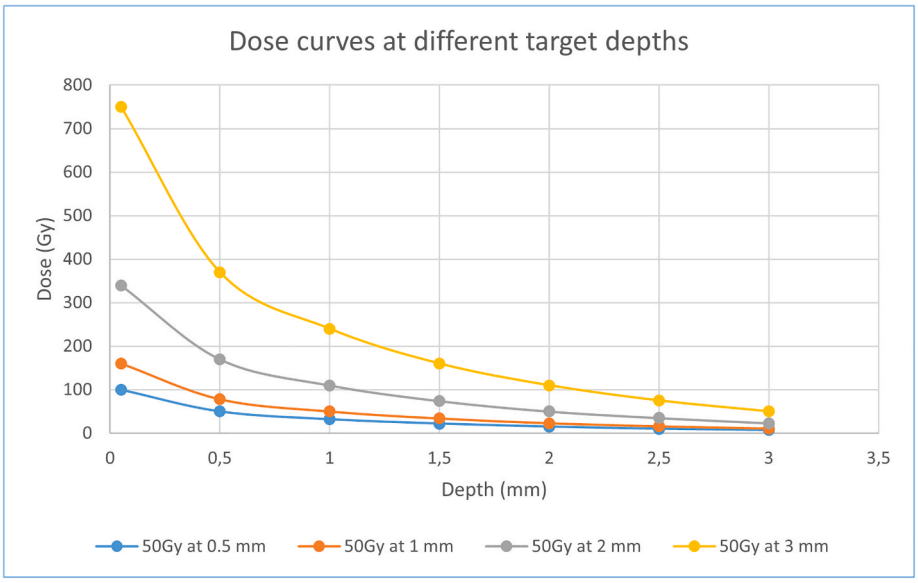


**Fig. 3.** Absorbed dose curves at different target depths at clinical depths (until 3 mm). Based on the data provided by OncoBeta.

beta emissions and scattered photon components. At superficial depths, the absorbed dose is predominantly driven by the beta component, as represented by the "only electrons without bremsstrahlung" curve (purple), which exhibits a rapid decline in dose with increasing depth. This steep attenuation indicates that the beta radiation contribution is primarily localized within the more superficial tissue layers.

As depth increases, the contribution of the 155 keV photon component (blue curve) becomes more significant, characterized by a slower rate of attenuation compared to the beta component. This is due to the greater penetration capacity of photons compared to emitted electrons. Beyond approximately 3–5 mm depth, the absorbed dose attributed to photon scatter surpasses that from beta electrons, emphasizing the increasing role of photons at greater depths.

*Implications for radiation protection*

Ensuring the radiological safety of both patients and medical staff is of paramount concern in the administration of $^{188}$Re. Comprehensive protection measures, including the use of a 10 mm thick Perspex screen to shield the physician from beta radiation during the application phase (1–3 min) to the patient, are necessary. The strategic deployment of shielding materials, such as lead, further enhances the therapeutic environment's safety, ensuring that $^{188}$Re procedures adhere to the highest standards of radiation protection. Additional radiation protection measures, such as lead aprons and protective eyewear, are recommended primarily due to the bremsstrahlung radiation generated by beta particles, which includes a low-energy photon component. Although $^{188}$Re emits 155 keV photons with a ~15 % abundance, standard lead aprons provide limited attenuation at this energy. Nonetheless, they offer partial shielding against bremsstrahlung, particularly for close-range handling of unshielded sources. This would ensure adequate protection for staff. Users must be cautious in this regard and take these considerations into account when handling $^{188}$Re.

It is important to emphasize that the $^{188}$Re resin is an unsealed radioactive source. As such, there is a potential risk of contamination during the preparation, application, and removal phases. This includes possible contamination of the brush, protective foil, patient skin—both

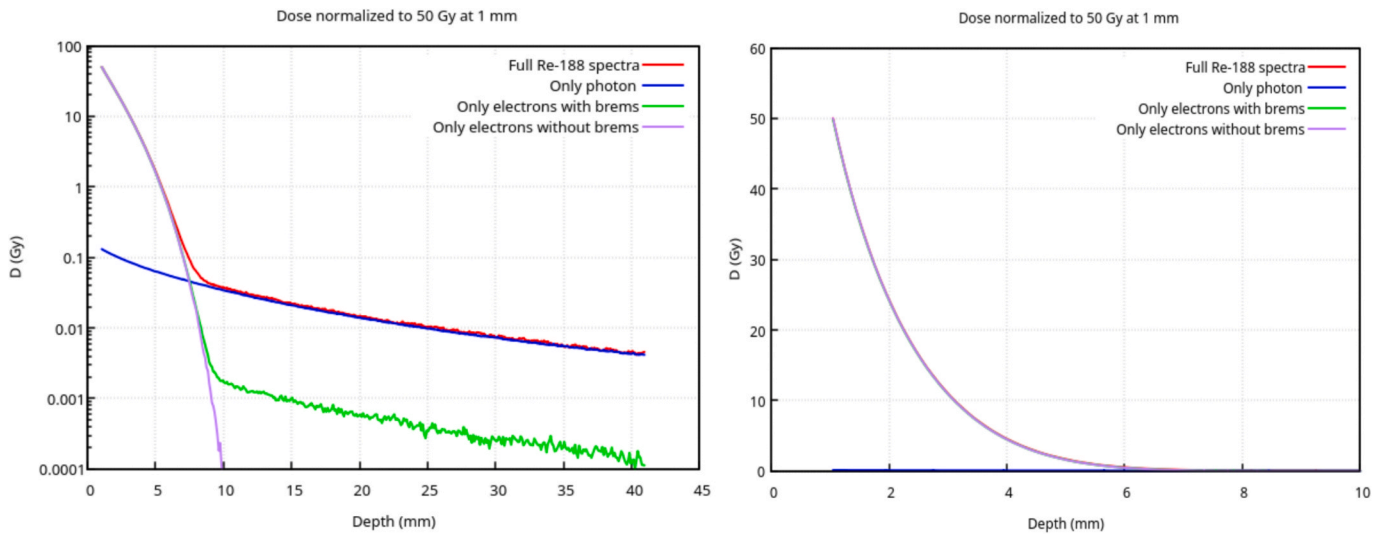


**Fig. 4.** Absorbed dose normalized to 50 Gy at 1 mm simulated by Monte Carlo. a – logarithmic scale, b – linear scale. D – Dose, brems – bremsstrahlung (breaking radiation). The Monte Carlo simulation was performed using PENELOPE-2018 [Salvat, F. (2019). Penelope 2018: A code System for Monte Carlo simulation of Electron and Photon Transport. OECD/NEAS Data Bank, Issys-les-Molineaux, France.]. It involves a 3x3 $cm^2$ water patch with a thickness of 0.1 cm emitting the Re-188 spectrum isotropically, incident on an adjoining infinite water block. Dose was simulated using 5x5x0.1 $mm^3$ voxels up to a depth of 40 mm.

under and around the lesion—and the treatment environment. Therefore, radiation surveys using appropriate contamination monitors should be systematically performed on all relevant surfaces, instruments, and materials (e.g., brush and foil) immediately after treatment and prior to releasing the patient or the equipment. In radiation therapy protocols that utilize unsealed sources, meticulous attention must be paid to procedural details to mitigate the risks of radiation exposure to both patients and healthcare providers. Essential protective measures, such as specialized garments, have been effectively implemented to reduce staff exposure to less than 0.7 μSv per treatment session. There is insufficient data to provide definitive recommendations regarding radiation protection, however, protective eyewear for staff may be considered when handling the unsealed source at close range. For patients, if the lesion is close to ocular structures, individualized shielding—such as custom eye protectors—may be required to minimize exposure. Radiation exposure for patients during Rhenium-SCT® therapy is primarily attributed to the gamma emissions from $^{188}$Re. This exposure varies depending on the tumor's location, generally remaining between 50 and 100 μSv and peaking at 170 μSv [15].Therefore, despite the considerably lower levels of therapeutic radiation compared to natural background radiation, continuous vigilance and adherence to safety protocols are essential to ensure the well-being of all involved in the procedure.

### *Clinical outcomes*

The overview of published clinical studies with $^{188}$Re paste is listed in Table 1. It includes approximately 240 people from one single-arm trial [14], one single-arm pilot study [16]and six case series [13,15,17,18,22]. The results of the phase 4 EPIC trial (A study of Rhenium Skin Cancer Therapy for non-melanoma skin cancer) are awaiting [23]. Reported side effects were generally observed within 14 days after application. The acute skin toxicity was reported mild to moderate in most cases (grade 1 or 2 as per CTCAE v.5.0). Some patients have been reported to experience grade 3 skin toxicity. However, in all cases symptoms were resolved within 90 days after treatment. The only

**Table 1**
Summary of clinical studies using $^{188}$Re paste for superficial non-melanoma skin cancers.

| Study (Author, Year) | n (Lesions) / Age | Study Design | Dose Prescription / Depth | Local Control | Toxicity (Acute / Late) | Follow-up |
|---|---|---|---|---|---|---|
| Sedda et al. (2008) [13] | 53 lesionsAge: NR | Case series | ~50 Gy; depth ~2–3 mmSingle session in most cases | 100 % CR; no recurrences | Grade 1 erythemaNo late effects; excellent cosmesis | Mean 51 mo (20–72) |
| Carrozzo et al. (2013) [18] | 15 lesions (penile SCC) Mean: 66 y | Case series | 50 Gy; ≤3 mm depth1–7 sessions | 80 % CR; others salvaged surgically | Mild erythema, crustingNo functional loss | Mean 51 mo (12–84) |
| Carrozzo et al. (2014) [17] | 5 lesions (EMPD)Mean: 69 y | Case series | 50 Gy; genital skinTwo sessions per patient | 100 % CR after two sessions | Burning, erythemaNo late toxicity | Mean 34 mo (27–48) |
| Cipriani et al. (2017) [22] | 42–44 lesions (BCC/cSCC)Age: NR | Retrospective | 50 Gy; 3–5 mm marginMostly single session | 100 % CR (2 retreated for recurrence) | Minimal toxicityNo late effects | Mean ~ 9.5 mo |
| Castellucci et al. (2021) [14] | 50 lesionsMean: 81 y | Single-arm trial | 50 Gy; depth ≤ 2.5 mmSingle session | 98–100 % CR at 12–24 mo | 93 % G1–2; 7 % G3Mild atrophy, pigment change | Up to 33 mo |
| Cipriani et al. (2022) [15] | 52 lesions (NMSC/BD/EMPD)Mean: 71.7 y | Retrospective | 50 Gy; depth 0.3–0.6 mmSingle session | 100 % CR | Only radiodermatitisMild hypopigmentation | Median 10 mo |
| Tietze et al. (2023) [16] | 22 lesions (BCC/cSCC/BD)Median: 83 y | Pilot study | 50 Gy; depth ≤ 3 mmStandard protocol | 95–97.5 % CR at 12 mo | G1–2 dermatitis49% hypopigmentation | 12 mo |
| Zagni et al. (2023) [21] | 75 lesions (BCC/cSCC) Median: 82 y | Retrospective | 50 Gy; Rhenium-SCT® protocol | Complete control (no failures) | Less pain vs surgeryMild hypopigmentation | ~12 mo |

**Abbreviations**: CR = Complete Response; G = Grade; mo = months; NR = Not reported; Gy = Gray (unit of absorbed dose); SCC = Squamous Cell Carcinoma; BCC = Basal Cell Carcinoma; EMPD = Extramammary Paget's Disease; BD = Bowen's Disease.
Toxicity grading based on CTCAE v5.0 when specified.

late and permanent side effect that has been reported was a mild depigmentation of the treated area itself and the surrounding area [15]. No systemic side effects have been reported so far. Follow-up visits were usually arranged in about 3 months after treatment. Complete response after one cycle is reported to range between 86 % and 100 % [14,15] with the remaining patients having a complete response after a second cycle.

*Certificates and approvals*

Rhenium-SCT® is approved as a medical product in the European Union and CE (Conformité Européenne)-certified. In addition, the medical product is certified by the Australian Therapeutic Goods Administration.

The UK National Institute for Health and Care Excellence (NICE) has evaluated the use of epidermal radiotherapy with $^{188}$Re paste as a treatment for non-melanoma skin cancer [24]. The guidance published in 2024 highlights that this therapy offers a targeted approach, potentially reducing the risk of damage to surrounding healthy tissues. NICE's assessment points out that $^{188}$Re paste has shown efficacy in decreasing lesion size with minimal adverse effects, presenting a less invasive alternative to surgical procedures. Long-term follow-up results suggest a low recurrence rate, advocating for the integration of $^{188}$Re paste in treatment protocols for specific patient cohorts. NICE recommended further research to determine the full spectrum of applicability and to optimize treatment regimens. The institute's endorsement could lead to broader adoption and refinement of this therapeutic modality in clinical practice.

## Discussion

The choice between sealed and unsealed sources underscores a key element of treatment personalization. Sealed sources, traditionally used in skin radiotherapy due to their consistent dose delivery, encounter challenges in conforming to the irregular and complex surfaces of skin and skin lesions. This is due to the fact that they are not in direct contact with the skin and that their application requires shielded applicators or a bolus to prevent overdosing of the skin surface or the problem of adapting to the curvature [25]. The advent of unsealed $^{188}$Re sources in dermato-oncology presents a significant shift, enabling the radiation source to conform precisely to the anatomical specifics of each lesion, ensuring uniform coverage of the therapeutic dose across the entire target area but with limitation as for the depth of penetration meaning only relatively superficial skin cancers can be considered for $^{188}$Re treatment.

The treatment protocol for $^{188}$Re treatments includes precise delineation of tumor boundaries, implementation of radiation protection measures and meticulous handling and disposal of the radioactive substance [14,22].

Given its physicochemical properties, $^{188}$Re paste is classified as an unsealed radiation source. These properties do not allow for $^{188}$Re categorisation as BT. According to the International Atomic Energy Agency (IAEA), BT traditionally involves the use of sealed radioactive sources placed either adjacent to or within a tumor [26]. Likewise, GEC-ESTRO defines BT as a localized form of irradiation delivered by sealed sources [27]. Since $^{188}$Re is applied in paste form and uses an unsealed-source radiation once exited from the sealed applicator, it does not align with these definitions.

In light of these distinctions, it is challenging to classify $^{188}$Re treatments as BT under current terminology. While these treatments are highly valuable in the context of skin cancer therapy, further consensus and discussions are needed to determine their place within the framework of dermato-oncology and BT.

Critical to the implementation of this therapy is the involvement of a certified medical physicist. Their responsibilities encompass the verification of the source activity, calculation of treatment time in accordance with the source decay and the verification of calculation software tools, together with contamination control of patients and treatment environment and handling the radioactive waste. An additional concern relates to the measurement of administered activity. Although primary standards for $^{188}$Re are available [11,12], in clinical practice the activity is usually determined using a commercial dose calibrator provided by the manufacturer (OncoBeta®). However, it is well known that activity measurements for high-energy beta emitters are highly sensitive to the geometry of the measuring setup. In the case of $^{188}$Re resin, the 'brush-syringe-paste' system presents a complex and non-standard geometry. OncoBeta has developed its own specific calibration factors and measurement protocol, but to date, no independent documentation has been made available regarding the procedure or the accuracy of these calibrations. This introduces a significant source of uncertainty—both systematic and random—in the dosimetry chain, which deserves further investigation and transparency in future work. Furthermore, the contribution of the 155 keV photon component cannot be underestimated at depths beyond 3 mm under skin surface, where its absorbed dose surpasses that of beta emissions, indicating its significant role in deeper tissue layers as illustrated in Fig. 4. These photons exhibit a slower attenuation rate compared to beta particles, resulting in a substantial absorbed dose at greater depths. This dosimetric behaviour underlines the necessity for further research into clinical dosimetry, specifically to quantify and validate the contribution of these photon components in clinical settings. Such understanding is vital for ensuring patient safety. Moreover, the presence of a significant photon component at greater depths necessitates careful consideration regarding radiation protection in $^{188}$Re application. Ensuring adequate radiation safety protocols is paramount to mitigate the potential risks associated with the increased photon dose, especially considering the unsealed-source nature of $^{188}$Re. Thus, cautious implementation and thorough dosimetric verification are essential steps to maintain treatment efficacy while safeguarding both patients and healthcare professionals.

The selection of medical professionals authorized to administer this therapeutic approach depends on the individual country legislation. Given the malignant nature of the target lesions and the potential for both immediate and delayed adverse effects, radiation oncologists and nuclear medicine specialists are seen as the primary specialists responsible for overseeing treatment. Nonetheless, with appropriate training in the management and follow-up of such therapies, dermato-oncologists can also assume a role in the treatment's administration.

A paramount consideration in the administration of $^{188}$Re is the optimal application of the paste across the lesion (target area), underscoring the importance of the expertise and training of professionals in this process. While the necessity for technologists in this treatment modality remains to be fully determined, their involvement in specific capacities, subject to specialized training, may enhance the efficacy of the treatment.

It is imperative to emphasize that the characteristics of irradiation with $^{188}$Re, including maximum dose, prescription depth, and dose gradient, are markedly different from those associated with standard $^{192}$Ir. Whereas in contact BT with $^{192}$Ir, the maximum dose on the skin surface is limited by the use of a bolus to distance the source away from the skin, in $^{188}$Re irradiation the isotope is on a foil in direct contact with the skin. Thus, while for a typical treatment with $^{192}$Ir, 5 mm bolus and prescription depth at 3 mm, the maximum surface dose is below 150 % of the prescribed dose for a 6 × 6 cm clinical target area [28]. In contrast, for a 2 mm dose prescription depth irradiated with $^{188}$Re, the maximum surface dose can be higher than 500 % of the prescribed dose, as shown in Fig. 3. Consequently, the experience gained with HDR skin BT cannot be directly transferred to $^{188}$Re treatment.

The primary objective of this critical review is to address the use of $^{188}$Re unsealed source applications in skin radiotherapy and to clarify its current standing within the clinical setting. It is imperative to underscore that the indication for this therapy should not be established without a comprehensive multidisciplinary discussion that explicitly involves radiation oncologists and nuclear medicine specialists. Such

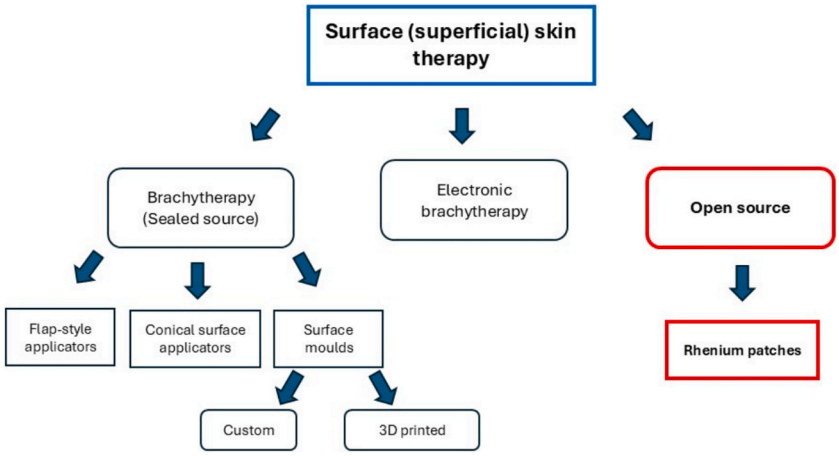


**Fig. 5.** Proposed position of $^{188}$Re among current radiation-based techniques used in surface (superficial or contact) therapy in dermato-oncology.

collaboration ensures that all therapeutic options are carefully considered, and patient care is optimized through the collective expertise of the treatment team.

The eight studies included in this review provide a consistent picture of the clinical efficacy and tolerability of $^{188}$Re paste (Rhenium-SCT®) for superficial non-melanoma skin cancers. The prescribed dose was generally ~50 Gy delivered to the lesion base, with effective penetration depths between 0.3 and 3 mm depending on tumor thickness and activity concentration [14–16,21]. In most studies, a single topical application was sufficient; however, selected cases required a second session, particularly in larger or histologically aggressive lesions [16,18].

Complete response rates ranged from 86 % to 100 %. Sedda et al. [13] and Cipriani et al. [22] reported 100 % complete remission after one or two sessions, with no local recurrences observed during follow-up. Castellucci et al. [14] and Tietze et al. [16] similarly reported complete responses in >95 % of lesions at 12 months. Carrozzo et al. [18] observed complete responses in 80 % of penile SCC patients after $^{188}$Re therapy, with the remaining cases successfully salvaged by surgery. In extramammary Paget's disease, Carrozzo et al. [17] achieved 100 % local control with two sessions per patient.

Acute toxicity was mostly limited to grade 1–2 radiodermatitis, including erythema, mild desquamation, and superficial ulceration, which resolved within 2–4 weeks [14,16,22]. Grade 3 toxicity was reported in a small minority of cases (7 % in Castellucci et al. [14]), with complete resolution within 10 weeks. No systemic toxicity or severe acute complications were described in any of the reviewed studies. Pain during or after treatment was consistently reported as minimal or absent [13,14,22], and no anesthesia was required.

The most frequently reported late side effect was hypopigmentation of the treated area, described by Cipriani et al. [15], Tietze et al. [16], and Zagni et al. [21]. No long-term ulceration, fibrosis, or secondary malignancies were observed. Cosmetic outcomes were rated good or excellent in all series, with high patient satisfaction scores [14,15,21]. In the comparative study by Zagni et al. [21], Rhenium-SCT® showed similar cosmetic results to surgery, but with lower pain scores and higher patient preference.

Overall, these findings support the effectiveness and safety of $^{188}$Re in well-selected cases of superficial NMSC. However, longer follow-up and prospective comparative data—such as those expected from the EPIC trial [23]—are needed to confirm durability of response and define its optimal role within dermato-oncology.

At this juncture, the clinical evidence supporting $^{188}$Re as a treatment modality is not sufficiently robust to advocate its use as an alternative to established therapies such as contact radiotherapy or other forms of radiotherapy in any clinical scenario. While preliminary studies may offer promising results, they are not adequate to substantiate the widespread adoption of $^{188}$Re without further rigorous investigation. Therefore, $^{188}$Re treatment should be considered experimental until more substantial evidence is available from larger scale randomized controlled trials.

The GEC-ESTRO Head and Neck and Skin and BRAPHYQS Working Groups recognize that while treatments using $^{188}$Re for skin cancer are frequently referred to as BT in the literature, $^{188}$Re does not align with the current definitions of BT, particularly HDR-BT. This is primarily due to the unique dosimetric properties of $^{188}$Re, which differ significantly from the sealed source radiation commonly employed in traditional BT.

The successful administration of $^{188}$Re treatments necessitates the involvement of a highly specialized team. This team must operate in strict accordance with national regulations, ensuring that all professionals involved in the radiation therapy process are properly qualified and licensed. A medical physicist with expertise in nuclear medicine and / or radiotherapy plays a pivotal role in $^{188}$Re application procedure, as their skills are essential for precise dosimetry calculations and the safe delivery of treatment. Their involvement guarantees that the therapeutic dose is accurately administered while safeguarding both the patient and medical staff.

Given the multidisciplinary nature of $^{188}$Re treatments, which involve collaboration between radiation oncologists, medical physicists, and nuclear medicine specialists, it becomes evident that this approach requires a framework that is distinct from conventional BT practices. While $^{188}$Re treatments offer valuable therapeutic benefits, particularly for superficial skin cancers, the current conditions and definitions of BT, specifically those involving sealed sources, make it challenging to classify $^{188}$Re within the traditional boundaries of BT and specifically not HDR BT.

Nonetheless, the continued integration of such treatments demands ongoing evaluation and a possible redefinition of terms to reflect the evolving nature of this emerging treatment.

## Concluding statements

The GEC-ESTRO Head and Neck and Skin and BRAPHYQS Working Groups, in the concluding statements of this critical review, affirms that:

- Although $^{188}$Re-based treatments for skin cancer are frequently discussed as a form of brachytherapy, they do not fully meet current classifications for BT and HDR-BT. This is primarily because these treatments use an unsealed radioactive source The application of $^{188}$Re requires a highly specialized, multidisciplinary team, whose composition must strictly adhere to national regulations governing the qualifications and roles of healthcare professionals in radiation therapy and nuclear medicine. A radiation oncologist should always be involved in the final decision, considering the possibility of treating the skin lesion with different radiotherapy techniques (external beam and brachytherapy (interventional radiotherapy)) to define the best radiotherapy approach based on the advantages and disadvantages of each technique.
- In particular, the involvement of a medical physicist with expertise in nuclear medicine and / or radiotherapy is critical. Their role ensures the precise calculation of dosimetry, the accurate delivery of radiation, and the overall safety and efficacy of the treatment process. This close collaboration between medical physicists, radiation oncologists, nuclear medicine expert and other specialists is essential for maintaining the high standards expected in radiation dermato-oncology.
- Given these factors, while $^{188}$Re treatments share some conceptual similarities with BT, the current dosimetric differences and delivery methods require to view these treatments within a distinct framework. Further discussion and adaptation of terminology may be necessary to accurately reflect the place of $^{188}$Re in the broader portfolio of radiation dermato-oncology.
- The review writing committee proposes the below position of $^{188}$Re treatment among current radiation-based techniques used in surface (superficial or contact) therapy in dermato-oncology (Fig. 5).

## CRediT authorship contribution statement

**Sergio Lozares:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Project administration, Supervision, Visualization. **Paula Tur:** Methodology, Formal analysis, Investigation. **Facundo Ballester:** Software, Validation, Formal analysis. **Ralph Alexander Bundschuh:** Methodology, Investigation, Validation, Writing – original draft. **Víctor González-Pérez:** Methodology, Investigation, Validation, Writing – original draft. **Ramin Jaberi:** Methodology, Investigation, Validation, Writing – original draft. **Javier Vijande:** Methodology, Software, Resources, Writing – original draft, Formal analysis. **Renate Walter:** Methodology, Investigation, Validation, Writing – original draft. **Åsa Carlsson Tedgren:** Resources, Supervision, Validation, Writing – review & editing. **Luca Tagliaferri:** Resources, Supervision, Validation, Writing – review & editing. **Frank-André Siebert:** Resources, Supervision, Validation, Writing – review & editing. **Agata Rembielak:** Resources, Supervision, Validation, Writing – review & editing, Conceptualization, Investigation, Project administration, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

JV acknowledges the Conselleria de Educación, Universidades y Empleo (GVA), grant CIPROM/2021/64, the Grant PID2021-125096NB-I00 funded by MCIN/AEI/ 10.13039/501100011033 and by "ERDF A way of making Europe" by the "European Union NextGenerationEU/ PRTR".

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