Interventional procedure overview of epidermal radiotherapy using rhenium-188 paste for non-melanoma skin cancer

Contents

Table 1 Abbreviations

Abbreviation	Definition
BCC	Basal cell carcinoma
CTCAE	Common Terminology Criteria for Adverse Events
EMPD	Extramammary Paget's disease
EBRT	External beam radiation therapy
NMSC	Non-melanoma skin cancer
RTOG	Radiation Therapy Oncology Group criteria scale
SCC	Squamous cell carcinoma
SCT	Skin cancer therapy
SD	Standard deviation

Indications and current treatment

NMSC is the most common type of cancer. It affects the cells in the top layers of the skin. The most common types of NMSC are BCC and SCC. The main symptom is the appearance of lesions (lumps or discoloured patches) on the skin. The lesions are most commonly found on skin that is regularly exposed to the sun.

The current standard of care within the NHS depends on the initial presentation of non-melanoma skin cancer, such as the type, size and location of the lesion. Surgery is the main treatment. Other treatment options include chemical therapies, cryotherapy, brachytherapy, external beam radiotherapy and photodynamic therapy.

What the procedure involves

The procedure is done without the need for anaesthesia or inpatient admission. It uses a beta-emitter radioisotope rhenium-188, which can penetrate the human tissue up to 3 mm deep. The rhenium-188 is bound to a matrix to form a paste

and is applied using a specially designed applicator. During the treatment, the area to be treated is protected from direct contact with the paste by a cream or sterile transparent foil. The rhenium-188 paste is then applied on the area of the lesion with a safety margin. The treatment time is calculated based on the applied radioactivity and the area of the region being treated and is typically about 30 to 180 minutes. The paste dries out during the treatment time and turns into a flexible film. The film is removed when the treatment is over. The dead cancer cells are gradually replaced with new healthy cells.

Unmet need

NMSCs are the most common class of skin cancers. The most common treatment is surgery. Surgery may lead to scarring if treating large or multiple lesions. Surgery or alternative therapies (chemical therapies, cryotherapy, brachytherapy, external beam radiotherapy and photodynamic therapy) may also be technically difficult in some common lesion sites, for example on fingers, ears or the nose. This procedure may offer a treatment option when surgery is not advised because of comorbidities or contraindicated, or for lesions which the anatomical position may result in a suboptimal cosmetic result using conventional approaches. Rhenium-188 paste can be used on genital lesions. Avoiding surgery on these lesions may be beneficial for preserving sexual function and quality of life.

Outcome measures

The main efficacy outcome is remission status. Four studies determined remission status with dermoscopic or histological assessment (Carrozzo, 2013; Carrozzo, 2014; Castellucci, 2021; Cipriani, 2022); 3 studies did not report the method used to determine remission status (Cipriani, 2017; Sedda, 2008; Tietze, 2023).

One study used the CTCAE to grade early skin toxicity (v5.0, Castellucci, 2021). This tool presents sets of criteria against each category of adverse event or symptom that is commonly caused by cancer treatments (for example, erythema). The criteria enable clinicians to make standardised assessments of the severity of the adverse event against descriptions of the event. The descriptions are marked against graded severity ratings from grade 1 (mild) to 5 (death related or due to adverse event).

One study used the RTOG to evaluate cosmetic results (Castellucci, 2021). This scale describes cosmetic changes to the skin. It ranges from poor (for example, ulceration or necrosis) to excellent (for example, no changes or slight pigment change). One study used an adapted version of this scale, in which definitions were amended to reflect treatment outcomes for rhenium-188 paste treatment in comparison with expected outcomes with surgery (Tietze, 2023). For example, a grade 1 (excellent) outcome was defined as “lesion not or barely detectable anymore, and/or much better than expected result after successful surgery”.

Evidence summary

Population and studies description

This interventional procedures overview is based on publications reporting on the safety and efficacy outcomes of approximately 240 people with NMSC from 1 single-arm trial of 50 people (Castellucci, 2021), 1 single-arm pilot study (Tietze, 2023) and 5 case series (Carrozzo, 2013; Carrozzo, 2014; Cipriani, 2017; Cipriani, 2022; Sedda, 2008). All patients had the procedure. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 8 published studies as the key evidence in table 2 and table 3.

The single-arm trial of 50 people and the single-arm pilot study were the only prospective studies (Castellucci, 2021; Tietze, 2023). Six of the key studies were done in Italy, 1 was done in Germany (Tietze, 2023). Of the key studies, 4 included people from the same hospital. Not all studies reported the dates that participants had treatment. All key studies done in Italy included at least one author that co-authored at least one other publication included in this overview. There may be some overlap in participants included in these studies. The single-arm pilot study (Tietze, 2023) is part of the ongoing EPIC-SKIN trial (NCT05135052).

The average age of people with NMSC considered for efficacy outcomes was between 66 and 83; 2 of the published studies did not report the ages of participants in their study (Cipriani, 2017; Sedda, 2008). Follow up was a mean of 20 months (range: 3 to 33 months) in the single-arm trial of 50 people (Castellucci 2021) and up to 12 months in the single arm pilot trial of 22 people (Tietze, 2023). Among the case series, mean follow-up was between 288 days (approximately 9.5 months) and 51 months. It was unclear whether the reported follow up points were after the last treatment received or if further treatment sessions were done during follow-up in some studies.

Whether lesions had been previously treated, which therapies were applied to lesions if previously treated and the type and size of lesions treated with rhenium-188 paste varied between and within studies. The most common type of lesion was BCC but most studies also included SCCs and sometimes EMPD and Bowen's disease. One study only included people with EMPD (Carrozzo, 2014) and one study only included people with SCC (Carrozzo, 2013). Most studies included some people with lesions that were previously treated with another intervention. Most studies included lesions located anywhere on the body but most were on the head and neck. Two studies only included people with lesions on the genitalia (Carrozzo, 2013; Carrozzo, 2014). Across studies, average

lesion size was between 1.25 and 10 cm^2 but ranged from 0.3 to 65 cm^2. Lesion depth was between 0.1 to 2.5 mm across studies. Two studies did not report the size or depth of lesions included in their analysis.

In the single-arm trial (Castellucci, 2021), 18 out of 60 lesions had already been treated with other therapies and relapsed (5 lesions had previous surgery; 2 lesions had previous surgery and photodynamic therapy or cryotherapy; 10 lesions had previous cryotherapy, laser and photodynamic therapy; 1 lesion had previous imiquimod) while 42 lesions were new diagnoses at presentation. In this study, 68% of lesions were BCCs, 30% were SCCs and 1 lesion was BCC and SCC. Lesions were mostly on the face, ears, nose and scalp (77%) and the remaining on extremities (15%) and trunk (8%). The mean surface area of lesions was 7 cm^2 (1 to 36 cm^2) and the mean depth was 1.1 mm (0.2 to 2.5 mm). This was not the largest lesion size among the studies (based on the mean lesion size and the maximum lesion size included) but they did treat the deepest lesions compared to other studies. The authors suggested that the size of lesions treated in their study may explain some of their grade 3 side-effects.

In the single-arm pilot study of 22 people (Tietze, 2023), 58% of lesions were BCC, 30% were Bowen's disease and 12% were SCC. Median lesion size was 1.25 cm^2 (range 0.04 to 16.8 cm^2). Lesion depth ranged from 0.1 to 2.1 mm, with a median of 0.35 mm. There were 40 lesions across the head, neck, trunk and lower extremities, and 13 had been previously treated with imiquimod, with unsuccessful surgery or diclofenac gel and curettage.

In the case series of 53 people, 28% of lesions had previous surgical treatment (Sedda, 2008). Lesions were diagnosed as BCC (70%) and SCC (30%) and mostly on the head and neck (70%). Other lesions were on the upper and lower limbs (22%) and trunk and back (8%). The mean size of lesion was 7 cm^2 (SD=8.9). The depth of lesions was not reported.

In the case series of 52 people, 54% of lesions had previous surgery or other intervention (Cipriani, 2022). Most lesions were BCCs (58%) but SCCs (35%) and 4 lesions diagnosed as Bowen's disease (n=2) and EMPD (n=2) were also treated. Most commonly, lesions were on the head and neck (73%) or genitalia (15%). Average lesion size was 10 cm^2 (range between 0.3 and 61 cm^2) and depth was between 0.3 and 0.6 mm.

In the case series of 43 people, 26% had previous surgery (Cipriani, 2017). Lesions were mostly BCCs (67%) and the rest were SCCs. Lesions were mostly located on the head and neck (65%) but lesions on the back, arm, leg, and penis were also treated. Median lesion size was 3 cm^2 (range 1 to 49 cm^2). Two lesions were deeper than 0.5 mm.

All participants in the case series of 15 people (Carrozzo, 2013) had previous topical therapy for SCC lesions located on the penis. One lesion was also previously treated with imiquimod and 5-fluorouracil and 2 with surgery. The size of lesions treated in this study was not reported.

In the case series of 5 people (Carrozzo, 2014), 80% of the participants had previous topical treatments for lesions. All 5 lesions were EMPD located on the genitalia. The size of lesions was not reported.

Table 2 presents study details.

Figure 1 Flow chart of study selection

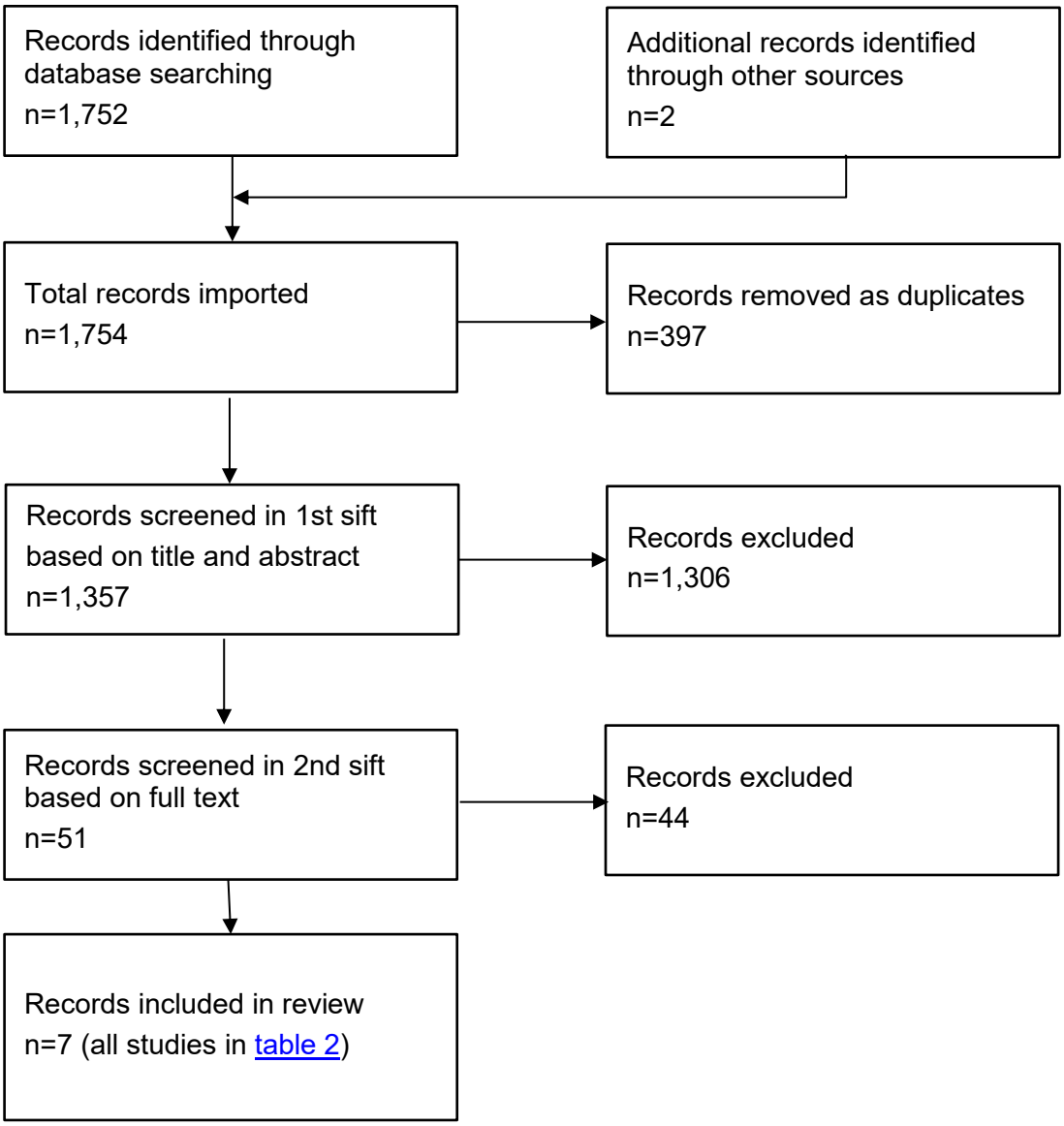

Table 2 Study details

Study no.	First author, date country	Patients (male: female)	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
1	Castellucci, 2021, Italy	n=50 (70% male, 30% female) 60 histologically proven NMSCs (n=41 BCC; n=18 SCC; n=1 BCC and SCC)	Mean=81	Single-arm trial October 2017 to January 2020	1) histologically proven BCC or SCC; (2) lesion thickness invasion less than 2.5 mm; (3) lesions located in the scalp, face, ears, or fingers or other areas in which surgery, EBRT or standard brachytherapy would have been difficult; (4) contraindication or refusal of surgery	Rhenium-188 brachytherapy using Rhenium-SCT (Oncobeta GmbH, Germany) Results were evaluated after 1 treatment session.	Mean 20 months (range 3 to 33)
2	Tietze, 2023, Germany	n=22 n=40 lesions (58% BCC, 30% Bowen's disease, 12% SCC)	Median=83	Single-arm pilot study November 2020 to April 2021	Histologically confirmed NMSC with surface area of 5 cm^2 or smaller and thickness of 3 mm or less, 18 years or older, not suitable or willing to undergo surgery. People were excluded if they had a known primary	Rhenium-188 brachytherapy using Rhenium-SCT Results reported after 1 session.	Up to 12 months

Study no.	First author, date country	Patients (male: female)	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
					melanoma near the treatment area or having treatment for metastatic or non-resectable melanoma.		
3	Sedda, 2008, Italy	n=53 (55% male, 45% female) n=37 BCC; n=16 SCC n=9 had multiple BCCs; n=3 had multiple SCCs	Not reported	Case series	Histologically confirmed BCC or SCC; relapse of tumour or surgery considered impossible or aesthetically unacceptable.	Rhenium-188 brachytherapy 43 people had 1 treatment session, 8 people had 2 and 2 people had 3 treatment sessions.	Mean 51 months (range 20 to 72)
4	Cipriani, 2022, Italy	n=52 (65% male, 35% female) n=55 lesions which included 32 BCC, 2 SCC, 2 Bowen's disease, 2 EMPD	Mean=71.7	Retrospective case series 2005 to 2014	Histologically confirmed BCC, SCC, Bowen's disease or EMPD	Rhenium-188 brachytherapy using Rhenium-SCT Results were evaluated after 1 session.	Mean=414 days; Median= 296 days
5	Cipriani, 2017, Italy	Unclear; n=42, 43 and 44 reported in different parts of the full-text	Not reported	Retrospective case series	Histologically confirmed NMSC; complete histological record, dosimetry	Rhenium-188 brachytherapy	Mean 288 days (range 35

Study no.	First author, date country	Patients (male: female)	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
		(approximately 58% male, 42% female) n=87 histologically confirmed lesions including BCC and SCC. 1 patient had Bowen's disease.			information and imaging material	Fractionated treatment was planned for people with lesions on lips and genitalia across 2 or 3 sessions. Otherwise responses reported after 1 session.	to 1,150 days)
6	Carrozzo, 2013, Italy	n=15 (100% male)	Mean= 66	Case series June 2005 to April 2010	Confirmed diagnosis of SCC of penis	Rhenium-188 brachytherapy using Rhenium-SCT (ITM, Germany) Up to 7 sessions. Some people had multiple sessions to treat different lesions.	Mean 51 months (range 12 to 84 months)
7	Carrozzo, 2014, Italy	n=5 (20% male; 80% female)	Mean=69	Case series First treatment sessions were	Clinical diagnosis of EMPD	Rhenium-188 brachytherapy using Rhenium-SCT (ITM, Germany)	Mean 34 months (range 27 to 48)

Study no.	First author, date country	Patients (male: female)	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
		80% primary EMPD; 20% secondary		between 2008 and 2010		1 session unless relapsed.	

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Castellucci, 2021	**Complete response at 6 months**=98% (53/54 evaluable lesions; total sample included 60 lesions) Partial response in 1/54 lesions (there was a small residual lesion, which was surgically excised with good cosmetic results). **Lesions free from relapse at 12 months=100%** (41/41 evaluable lesions) **Lesions free from relapse at 24 months=96%** (23/24 evaluable lesions) 1 lesion required retreatment within 24 months. **Cosmetic results 12 to 33 months after 1 session (RTOG scale)** • Excellent= 73% (30/41) • Good= 27% (11/41)	No notable pain during or after treatment. 93% (56/60) of lesions showed early localised side-effects (grades 1 to 2 according to CTCAE 5.0) including skin erythema, faint or moderate oedema and ulcerations. These resolved in a mean of 4 weeks. 7% (4/60) of lesions showed more severe (grade 3 according to CTCAE 5.0) early side effects which resolved within 90 days (mean=10 weeks). Late side effects (3 to 33 months) included dyschromia, slight skin atrophy, hair loss. These were not considered clinically significant.

First author, date	Efficacy outcomes	Safety outcomes
Tietze, 2023	**Clinical outcome at 4 months** • 5/40 lesions were considered suspicious. • A biopsy was taken of 1 of the 5 suspicious lesions which showed that it was still malignant. This lesion had reduced by 75% in size but had a thickness of 3.8 mm and should have been excluded at baseline. The lesion was excised. **Clinical outcome at 12 months** • 97.5% (39/40) of lesions had responded; 95% had complete response. • 3/39 lesions were considered suspicious; biopsies were taken of all 3 which confirmed that 1 was Bowen's disease. • The malignant lesion was on the edge and outside of the previously radiated area, so the authors reported it was possibly not a residual/recurrent disease but a newly developed Bowen's disease. This lesion was excised. • 1 person died from an unrelated cause before 12-month follow-up **Cosmetic outcome at 4 and 12 months (RTOG scale)** • 85% (34/40) were graded as excellent,	No adverse events were reported during or immediately after treatment; 62.5% of lesions had no associated adverse events at any time point. All adverse events were grade 1 except for 2 grade 2 pain events according to CTCAE 5.0. **14 days** • 20% (8/40) lesions were itching, • 12.5% (5/40) lesions were painful, • 7.5% (3/40) lesions had a burning sensation, • 97.5% (39/40) lesions had signs of radiodermatitis (erythema, scabs, erosions; 65% of these were grade 2 and 32.5% were grade 1). Grade of radiodermatitis was not associated with adverse event reporting but was associated with the thickness of the lesion and the applied activity. **4 months** • 7.5% (3/40) lesions were itching, • 5% (2/40) lesions were painful, • 2.5% (1/40) lesions were ulcerated, • 25% of lesions showed hypopigmentation. **12 months**

First author, date	Efficacy outcomes	Safety outcomes

	• 13% (5/40) were graded as good,
	• 2.5% (1/40) was graded as poor because of ulceration,
	• Cosmetic outcomes were the same at 12 months as at 4 months.
	
	Cosmetic outcome at 4 and 12 months (adapted RTOG scale which compares against expected surgery outcomes)
	• At 4 months:
	  ○ 22.5% (9/40) were graded as excellent
	  ○ 57.5% (23/40) were graded as good
	  ○ 17.5% (7/40) graded as acceptable
	  ○ 1 (2.5%) was graded as poor
	• At 12 months scores had significantly improved (p=0.03):
	  ○ 41% (16/39) were graded as excellent,
	  ○ 51.3% (20/39) were graded as good,
	  ○ 7.7% (3/39) were graded as acceptable ,
	  ○ No lesion was graded as poor.
		• 2.5% (1/40) lesion was still ulcerated but almost completely healed after treatment.
		• 49% of lesions showed hypopigmentation.

First author, date	Efficacy outcomes	Safety outcomes
	• Between 4 and 12 months, the grading of 3 lesions deteriorated because of increased hypopigmentation.	
Sedda, 2008	**Complete clinical remission=** 100% (53/53) at 3 to 5 months after treatment (43 people had 1 treatment session, 8 people had 2 and 2 people had 3 treatment sessions) There were no relapses within 20 to 72 month follow up. **Complete healing**= 100% (53/53) after 20 to 72 months (mean= 51 months) and up to 3 sessions. No disfiguring scarring. Histological analysis, available for about 60% of patients, confirmed complete tumour regression after the treatment (timing not reported).	Erythema in irradiated area which disappeared after 2 to 7 days. Bleeding in large lesions which stopped and formed a scab 10 to 30 days after treatment. No pain. No systemic or topical side-effects. No measurable radioactive contamination. No longer term side effects.
Cipriani, 2022	**Complete remission= 100%** (52/52) of people after 1 session. Remission was sustained throughout follow up (median= 296 days; 27% (14/52) people were lost to follow up and may not have been included in this figure).	10% (5/52) died after 1 year of treatment. Cause of death was not reported. Slight depigmentation of the treated region. No other complications or post-interventional problems.

First author, date	Efficacy outcomes	Safety outcomes
		No radioactivity contamination of patients, staff or equipment
Cipriani, 2017	**Complete remission at follow up=100%** (mean follow up 288 days (range 35 to 1,150 days, median 212 days; 1 person was lost to follow up). 5% (2/43) required unplanned retreatment because the security margin was too tight, resulting in a recurrence at the border of the treated area. All achieved full remission after this. Radiation wounds healed within 30 to 154 days (median=53 days).	Some lesions produced clear serum for 1 to 2 weeks after treatment but stopped without further intervention. No other side effects or adverse events during or between 30 and 154 days after treatment. No pain during or after treatment. No haematological toxicity observed. No radioactivity contamination.
Carrozzo, 2013	**Complete remission at follow up=80%** (12/15) (mean 51 months; 1 person lost to follow up). 13% (2/15) required surgical salvage therapy.	Faint redness in irradiated area immediately after treatment. Erythema present after a few days. Serum secretion which formed a crust. Visual clinical healing in 3 to 4 months. The authors report no pain, discomfort or other side effects.
Carrozzo, 2014	**Complete remission at the end of treatment=100% (5/5)** Of the 5 patients,1 had 1 treatment session and 4 had 2 sessions; 2 of the 5 patients had relapse inside the treated area and 2 had relapse at the periphery of the previously treated area. Clinical healing in a mean of 34 months.	Faint redness in irradiated area immediately after treatment. Burning sensation and superficial erosions in days after treatment requiring topical or analgesic treatment. Erythema Serum secretion from wound which formed a scab and resolved in 2 to 3 weeks.

First author, date	Efficacy outcomes	Safety outcomes
		One patient, who had secondary EMPD, died from metastatic bladder cancer.

Procedure technique

Five studies named the device used to apply rhenium-188 paste to the skin (Carrozzo, 2013; Carrozzo, 2014; Castellucci, 2021; Cipriani, 2022; Tietze, 2023). All used the Rhenium-SCT kit. This device contains the radioactive material in an applicator and has a shield to protect the person applying the substance to the skin. All treatments were done within a nuclear medicine department or facility with appropriate licencing. Cipriani (2017) used a device that looks like the Rhenium-SCT kit but did not name it. Sedda (2008) gave no information on device or application tool.

All studies used materials to prevent direct contact between the radioactive material and the skin. One study (Sedda, 2008) used protective cream,5 studies used an adhesive plastic foil (Carrozzo, 2013; Carrozzo, 2014; Castellucci, 2021; Cipriani, 2017; Tietze, 2023) and 1 study used the cream and/or the foil (Cipriani, 2022).

All studies tailored the dose according to initial radioactivity, isotope emission energy, contact time and the size and depth of the lesion. Seven studies reported that they used at least one algorithm to calculate the dose required. Castellucci (2021) used a progressive reduction of delivered doses because of the incidence of early side-effects.

Most studies reported that radioactive substance was applied to an area which included the lesion and a border of healthy tissue. Carrozza (2013; 2014) used a margin of 2 to 4 mm. Cipriani (2017) used a margin of 3 to 5 mm. Castellucci (2021) used a margin of 3 mm. Cipriani (2022) used a margin of 5 mm.

Irradiation time varied within and between studies. Sessions lasted between 15 minutes and 2 hours in Sedda (2008) and Cipriani (2017). Carrozzo (2013; 2014) both reported sessions lasted between 30 minutes and 1 hour. Castellucci (2021) reported sessions lasted between 21 and 285 minutes and Cipriani (2022)

reported sessions lasted between 8 and 240 minutes. In the single-arm pilot study, Tietze (2023) reported sessions lasted between 38 to 175 minutes.

The number of sessions and reasons for multiple sessions varied between studies. Details are presented under efficacy outcomes in terms of relapse and reintervention rates.

Efficacy

Complete remission

All 7 studies reported data on remission. Complete remission ranged from 80% to 100%.

In the single-arm trial of 50 people with 60 lesions, 54 lesions were followed up 6 months after 1 treatment session and 98% showed complete response to treatment (Castellucci, 2021). Partial response was observed in 1 lesion.

In the single-arm pilot study of 22 people with 40 lesions (Tietze, 2023), complete response was seen in 95% of lesions at 12 months; partial or complete response was seen in 98% of lesions.

In the case series of 53 people, 100% (53/53) were in apparent complete clinical remission after 3 to 5 months (Sedda, 2008). 81% (43/53) were treated with 1 session, 15% (8/53) with 2 sessions and 4% (2/53) with 3 sessions.

In the case series of 52 people, 100% (52/52) showed complete remission after 1 session (Cipriani, 2022).

In the case series of 43 people, 100% (43/43) showed complete remission between 35 and 1,150 days after treatment (median=212 days; Cipriani, 2017). This included 2 people (5%) whose lesions needed unplanned retreatment because of recurrence at the border of the treated area.

In the case series of 15 people with SCC of the penis, complete remission was observed in 80% (12/15) of people, 13% (2/15) of lesions did not respond to therapy and 1 person was lost to follow-up (Carrozzo, 2013). Lesions were treated in up to 7 sessions and mean length of follow-up was 51 months.

In the case series of 5 people, all 5 showed complete remission after a mean follow up period of 34 months (Carrozzo, 2014). Lesions were treated with 1 session in 1 person, and with 2 sessions in 4 people. Retreatment was triggered by partial response in these 4 people.

Relapse

In the single-arm trial of 50 people including 60 lesions treated in 1 session, 100% of people who were followed up (41/41) were still in remission at 12 months (Castellucci, 2021) and 96% of those who were followed up (23/24) were still in remission at 24 months. One lesion needed retreatment by 24 month follow up.

In the single-arm pilot study of 22 people with 40 lesions (Tietze, 2023), there was 1 lesion that had Bowen's disease at 12 months. The authors reported that it was on the edge and outside of the previously radiated area, so they said it was possibly not a residual or recurrent disease but newly developed Bowen's disease.

In the case series of 53 people, there were no relapsed cases after 20 to 72 months (mean=51; Sedda, 2008). Lesions were treated in up to 3 sessions. The authors did not report whether additional sessions were planned or triggered by recurrence.

In the case series of 52 people, there were no relapsed cases after a median follow-up of 296 days (Cipriani, 2022). This figure may not include 14 patients

that were lost to follow-up. They reported 10% (5/53) of people died after the first post-interventional year and reason for death was not reported.

In the case series of 43 people, fractionation of treatment across 2 or 3 sessions was planned for people with lesions on their lips or genitals. Further treatment was triggered in some cases by recurrence at follow up (Cipriani, 2017). They reported that 5% (2/43) of people needed unplanned retreatment with rhenium-188 paste. All had full remission after retreatment.

In the case series of 15 people with SCC of the penis, lesions were treated in up to 7 sessions (Carrozzo, 2013). It was unclear whether retreatment was triggered by partial response or recurrence which required further intervention or if this was planned. Some people with SCC of the penis were treated in different locations in different sessions. They reported that 13% (2/15) required surgical salvage therapy because of non-response. Results were reported at a mean follow-up of 51 months. One participant was lost to follow-up.

In the case series of 5 people, relapse triggered a second session of therapy in 4 of 5 people (Carrozzo, 2014). After retreatment, all 5 were in complete remission at a mean of 34 months follow-up.

Healing and cosmesis

In the single-arm trial of 50 people with 60 BCC and SCC lesions, RTOG criteria were used to evaluate cosmetic results 12 to 33 months after 1 session (Castellucci, 2021). Of 41 evaluable lesions (68% of original sample), 73% (30/41) were rated excellent and 27% (11/41) were rated good.

In the single-arm pilot study of 22 people (Tietze, 2023), cosmesis was measured on RTOG criteria and an adapted version of RTOG which included a comparison against expected surgical outcomes. According to the standard RTOG criteria, 85% were graded as excellent, 13% as good and 1 lesion as poor because it

showed ulceration. This was the same at 4 and 12 months. According to the adapted RTOG scale at 4 months, 23% were graded as excellent compared to expected surgical outcomes, 58% as good, 18% as acceptable and 1 lesion as poor. At 12 months these had significantly improved (p=0.03). 41% were graded as excellent, 51% as good, 8% as acceptable and no lesion graded as poor. Between 4 and 12 months, the grading of 3 lesions deteriorated because of increased hypopigmentation.

In the case series of 53 people, the authors reported no disfiguring scarring after 20 to 72 months (mean=51 months) and that all lesions had completely healed after up to 3 sessions (Sedda, 2008).

In the case series of 52 people with lesions treated in 1 session, slight depigmentation was observed (Cipriani, 2022).

In the case series of 43 people, radiation wounds were observed between 30 and 154 days after treatment (Cipriani, 2017). These healed without medical intervention. The authors reported that treatment leaves no scar but in some cases faint discolouration of the skin is present.

In the case series of 15 people with SCC of the penis, visual and clinical healing was reported 3 to 4 months after treatment (Carrozzo, 2013).

In the case series of 5 people, complete healing was observed after a mean of 34 months follow up (Carrozzo, 2014).

Safety

In the single-arm trial of 50 people with 60 BCC and SCC lesions, CTCAE 5.0 was used to assess early skin toxicity within the first 30 days of 1 session of treatment in all 60 lesions (Castellucci, 2021). 93% (56/60) showed early side-effects (grades 1 to 2) including erythema, faint or moderate oedema and ulcerations. These resolved in a mean of 4 weeks. 7% (4/60) of lesions showed

more severe (grade 3) early side effects which resolved within 90 days (mean=10 weeks). No notable pain was reported during or after treatment. Late side-effects (3 to 33 months) included dyschromia, slight skin atrophy, hair loss. The authors did not consider these to be clinically significant side-effects.

In the single-arm pilot study of 22 people with 40 lesions (Tietze, 2023), CTCAE was used to assess adverse event grade at 14 days, 4 months and 12 months. There were no adverse events during or immediately after treatment and 63% of lesions had no associated adverse events. All adverse events were grade 1 except for 2 grade-2 pain events. Most adverse events were reported within 14 days and included: itching (20%), pain (13%) and burning sensation (8%). At 4 months, adverse events were less frequent, including: itching (8%), pain (5%), ulceration (1 lesion), hypopigmentation (25%). At 12 months, 1 lesion was still ulcerated and 49% of lesions showed hypopigmentation. Radiodermatitis was also graded according to CTCAE 5.0. Within 14 days, 98% of lesions showed signs of radiodermatitis, including erythema, scabs and erosions. Of these lesions with signs of radiodermatitis, 65% were grade 2 and 35% were grade 1. Grade of radiodermatitis was not associated with occurrence of reported adverse events, but was associated with thickness of the tumour.

In the case series of 53 people, erythema was reported in the irradiated area which disappeared after 2 to 7 days (Sedda, 2008). Bleeding was reported in large lesions which stopped and formed a scab 10 to 30 days after treatment. No pain, systemic or topical side-effects, measurable contamination or other longer-term side effects were reported.

In the case series of 52 people, the authors reported no other complications, post-interventional problems or contamination (Cipriani, 2022). They reported 9% (5/53) of people died after the first post-interventional year and reason for death was not reported.

In the case series of 43 people, the authors reported that some lesions produced clear serum for 1 to 2 weeks after treatment but stopped without further intervention (Cipriani, 2017). The authors reported that no pain, haematological toxicity, contamination or other side effects were observed during or after treatment.

In the case series of 15 people with SCC of the penis, faint redness in the irradiated area was observed immediately after treatment (Carrozzo, 2013). Erythema was present after a few days. There were 3 cases of serum secretion from the treated area which then formed a crust. The authors reported no pain, discomfort or other side effects.

In the case series of 5 people, there was faint redness in the irradiated area immediately after treatment (Carrozzo, 2014). The authors reported a burning sensation and superficial erosions in the days after treatment, requiring topical or analgesic treatment. Erythema was observed and some lesions secreted serum which later formed a scab.

Anecdotal and theoretical adverse events

The authors of the single-arm trial (Castellucci et al, 2021) stated that a longer observation period is needed to rule out the theoretical possibility of developing another (secondary) cancer in the local skin due to the radiation treatment.

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal and theoretical adverse events:

- infection
- skin burns
- dry skin
- alopecia
- skin induration
- hyperpigmentation
- telangiectasia
- secondary or late malignancy in treated region (up to decades later)
- delayed wound healing
- unintended exposure to other parts of the body
- keloids
- necrosis.

Four professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- The key evidence had a collective sample of 240 people. Each study had 53 participants or fewer.
- Of the 7 studies, 6 were done in Italy.
- Complete response was between 80% and 100%, indicating a consistent efficacy signal.
- The single-arm trial of 50 people was the largest prospective study (Castellucci, 2021) and had the longest follow-up (20 months) among the prospective studies included in the overview. The authors stated larger patient population and longer follow-up are needed to confirm the preliminary data and find the optimal dose needed to achieve complete response without significant side effects.

- The 5 retrospective case series did not have standardised follow up points and length of follow up varied widely within each sample (range: 288 days to 51 months). No studies reported reasons for loss to follow up.
- All 6 studies that were done in Italy had overlaps in the research groups. Four of the 6 studies were conducted in the same hospital and all 6 publications shared at least one author. The dates that people received treatment were not reported in some studies. This may mean that there is some overlap in participants.
- Five of the 7 study designs were case series and did not report a clear strategy for patient selection. Cases presented in these reports may have been subject to selection bias. The single-arm trial of 50 people and single-arm pilot study reported inclusion and exclusion criteria and a clearer protocol for patient identification (Castellucci, 2021; Tietze, 2023). However, the single-arm pilot study included information that indicated that the criteria were not adhered to (Tietze, 2023). The authors reported that 1 lesion that needed further surgical intervention after rhenium-188 paste was deeper than the inclusion criteria allowed and that this lesion should not have been included in the study. In addition, the largest lesion size was reported as being 16.8 cm^2 in this study, but the inclusion criteria stated that lesions were to be 5 cm^2 or less to be eligible for inclusion.
- Six studies included participants whose lesions were on different locations on the body. One study only included participants with lesions on the penis (Carrozzo, 2013). Five studies reported the surface area of the lesion and these appear to be similar. All studies included some participants whose lesions had previously been treated with another intervention before rhenium-188 paste.
- Studies used a mixture of histological, dermoscopic and 'clinical assessment' (not otherwise described) methods to determine response status. The single-arm trial of 50 people (Castellucci, 2021) was the only study that reported how

they classified response status. They used dermoscopy for all lesions and biopsy was used if needed. This and the single-arm pilot trial of 22 people (Tietze, 2023) were also the only studies that used standardised measures to assess cosmetic outcomes and severity of safety events. They were the only studies that reported the frequency of safety events. All 5 other studies described the types of adverse events that were observed but did not report the frequency. No study used patient reported outcome measures.

- There was some evolution of the procedure between the earliest (Sedda, 2008) and subsequent publications. The Rhenium-SCT kit was used to apply the radioactive resin in at least 6 studies. Different materials were used to protect the skin (cream only compared to foil or combination) and several versions of the software used to calculate how long to irradiate the lesion were used.
- One study pre-planned to fraction the dose across multiple sessions for lesions on the lips and genitals or for thicker lesions (Cipriani, 2017). Three studies delivered the intervention and reported outcomes after 1 session (Cipriani, 2022; Castellucci, 2021; Tietze, 2023). Three studies delivered multiple sessions for some participants (Carrozzo, 2013; Carrozzo, 2014; Sedda, 2008) but 2 did not state when they happened or whether they were pre-planned or triggered by partial or non-response to previous sessions (Carrozzo, 2013; Sedda 2008). Interpretation of treatment success and relapse is difficult in these studies.
- Some studies successfully treated large lesions but 5 studies commented that some recurrences related to size, depth of lesion and the success of the security margin mapped around the lesion.
- Castellucci (2021) did a statistical analysis that showed that grade 3 acute toxicity was significantly related to the surface area treated and the dose.
- Multiple authors on the Cipriani (2022) publication were employees, former employees or medical consultants for OncoBeta. OncoBeta were funded to

publish the paper. Tietze (2023) reports honoraria and funding from Oncobeta. Cipriani (2017) acknowledges support from OncoBeta, MAVIG GmbH and GBN Systems Gmb but do not state this is a conflict of interest.

- Ongoing trials:
  - The single-arm pilot study included in the main evidence (Tietze, 2023) is part of an ongoing study: Efficacy of Personalised Irradiation With Rhenium-Skin Cancer Therapy (SCT) for the Treatment of Non-Melanoma Skin Cancer: A Phase IV, Multi-Centre, International, Open-Label, Single Arm Study (EPIC-Skin; NCT05135052); Australia; n=210; study completion date May 2024.

Related NICE guidance

Interventional procedures

- NICE's interventional procedures guidance on electrochemotherapy for primary basal cell carcinoma and primary squamous cell carcinoma. (Recommendation: special arrangements).
- NICE's interventional procedures guidance on photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions).(Recommendation: standard arrangements for BCC, Bowen's disease and actinic (solar) keratosis; special arrangements for invasive squamous cell carcinoma).

Technology appraisals

NICE's technology appraisal guidance on cemiplimab for treating advanced cutaneous squamous cell carcinoma.

NICE's technology appraisal on vismodegib for treating basal cell carcinoma

Medical technologies

NICE's medical technologies guidance on Ambulight PDT for the treatment of non-melanoma skin cancer.

Diagnostics

NICE's diagnostics guidance on VivaScope 1500 and 3000 imaging systems for detecting skin cancer lesions

NICE guidelines

NICE guideline on suspected cancer: recognition and referral.

Cancer service guidelines

Improving outcomes for people with skin tumours including melanoma.

Professional societies

- Association of Cancer Physicians
- British Association of Dermatologists
- British Association of Plastic Reconstructive and Aesthetic Surgeons
- British Nuclear Medicine Society
- Royal College of Radiologists.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the interventional procedures team and any relevant points have been taken into consideration when preparing this overview.

References

1. Castellucci P, Savoia F, Farina A et al. (2021). High dose brachytherapy with non sealed 188Re (rhenium) resin in patients with non-melanoma skin cancers (NMSCs): single center preliminary results. *European Journal of Nuclear Medicine and Molecular Imaging, 48,* 1511-1521.

2. Tietze JK, Heuschkel M, Kronert MIC et al. (2023). Topical 188Re ionizing radiation therapy exerts high efficacy in curing nonmelanoma skin cancer. *Clinical Nuclear Medicine, 48*(10), 869-876.

3. Sedda AF, Rossi G, Cipriani C et al. (2008). Dermatological high-dose-rate brachytherapy for the treatment of basal and squamous cell carcinoma. *Clinical and Experimental Dermatology, 33*(6), 745-9.

4. Cipriani C, Desantis M, Dahlhoff G et al. (2022). Personalized irradiation therapy for NMSC by rhenium-188 skin cancer therapy: a long term retrospective study. *Journal of Dermatological Treatment, 33*(2), 969-975.

5. Cipriani C, Frisch B, Scheidhauer Ket al. (2017). Personalized High-Dose-Rate Brachytherapy with Non-Sealed Rhenium-188 in Non-Melanoma Skin Cancer. *International Journal of Nuclear Medicine Research,* 114-122.

6. Carrozzo AM, Sedda AF, Muscardin Let al. (2013). Dermo beta brachytherapy with188-Re in squamous cell carcinoma of the penis: a new therapy. *European Journal of Dermatology, 23*(2), 183–188.

7. Carrozzo AM, Cipriani C, Donati Pet al. (2014). Dermo beta brachytherapy with 188Re in extramammary Paget's disease. *Giornale Italiano di Dermatologia e Venereologia, 149*(1):115-21.

.

Methods

NICE identified studies and reviews relevant to epidermal radiotherapy using rhenium-188 paste from the medical literature. The following databases were searched between the date they started to 25 October 2023: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- Patients with non-melanoma skin cancer.
- Intervention or test: rhenium-188 paste.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE ALL (Ovid)	25/10/2023	1946 to October 24, 2023
EMBASE (Ovid)	25/10/2023	1974 to October 23, 2023
EMBASE Conference (Ovid)	25/10/2023	1974 to October 23, 2023
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	25/10/2023	Issue 10 of 12, October 2023
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	25/10/2023	Issue 10 of 12, October 2023
International HTA database (INAHTA)	25/10/2023	-

MEDLINE ALL search strategy

1 (("non melanoma*" or non-melanoma* or nonmelanoma*) adj4 skin adj4 (cancer* or tumo?r* or neoplasm* or carcinoma*)).tw. 6341
2 NMSC.tw. 1732
3 Carcinoma, Basal Cell/ 18811
4 (Basal Cell adj4 (Carcinoma* or Epithelioma*)).tw. 17082
5 (Rodent adj4 Ulcer*).tw. 202
6 Carcinoma, Squamous Cell/ 141619
7 ((Squamous or Epidermoid or Planocellular) adj4 carcinoma*).tw. 135389
8 (BCC or SCC).tw. 32956
9 (keratinocyte adj4 (cancer* or tumo?r* or neoplasm* or carcinoma*)).tw. 1042
10 or/1-9 227366
11 Rhenium/ 2185
12 ((Rhenium adj2 "188") or "Rhenium-188").tw. 308
13 Brachytherapy/ 21884
14 (brachytherap* or curietherap*).tw. 20846
15 13 or 14 28507
16 ((High adj4 dose) or HDR or (Dermo adj4 beta)).tw. 135219
17 15 and 16 6211
18 (((beta adj4 emitter) or epiderm*) adj4 radioisotope*).tw. 6
19 (radioactive adj4 resin*).tw. 45
20 11 or 12 or 17 or 18 or 19 8524
21 10 and 20 707
22 (Oncobeta or Rhenium-SCT).tw. 3
23 21 or 22 708
24 Animals/ not Humans/ 5129528

25	23 not 24	699
26	limit 25 to ed=20230428-20231031	6
27	limit 25 to dt=20230428-20231031	12
28	26 or 27	15