Medical Policy

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Title: Electronic Brachytherapy for Nonmelanoma Skin Cancer

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Populations	Interventions	Comparators	Outcomes
Individuals: • With nonmelanoma skin cancer	Interventions of interest are: • Electronic brachytherapy	Comparators of interest are: • Surgery • External beam radiotherapy • Standard brachytherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Treatment-related morbidity

DESCRIPTION

Electronic brachytherapy is a form of radiotherapy designed to deliver high-dose rate radiation to treat nonmelanoma skin cancer (NMSC). This technique focuses a uniform dose of X-ray source radiation to the lesion with the aid of a shielded surface application.

OBJECTIVE

The objective of this evidence review is to determine whether electronic brachytherapy improves the net health outcome in patients with nonmelanoma skin cancer.

BACKGROUND

Nonmelanoma Skin Cancer

Squamous cell carcinoma and basal cell carcinoma are the most common types of nonmelanoma skin cancer (NMSC) in the United States, affecting between 1 million and 3 million people per year[1,2,] respectively, and increasing at a rate of 3% to 8% per year.[2,] Other types (eg, T-cell lymphoma, Merkel cell tumor, basosquamous carcinoma, Kaposi sarcoma) are much less common. Skin cancer can affect anyone, regardless of skin color; however, the incidence of skin cancer among non-Hispanic White individuals is approximately 30 times higher than that among non-Hispanic Black or Asian/Pacific Islander individuals.[3,] In individuals with darker skin tones, skin cancer is often diagnosed at a later stage when it is more difficult to treat. Additionally, these individuals are prone to skin cancer in areas not commonly exposed to the sun such as the palms of the hands, soles of the feet, the groin, and inside of the mouth.

The primary risk factor for NMSC is sun exposure, with additional risk factors such as toxic exposures, other ionizing radiation exposure, and immunosuppression playing smaller roles.[2,] Although these cancers are rarely fatal, they can impact quality of life, functional status, and physical appearance.

Treatment

In general, the most effective treatment for NMSC is surgical. If surgery is not feasible or preferred, cryosurgery, topical therapy, or radiotherapy can be considered, though the cure rate may be lower.[4,] When considering the most appropriate treatment strategy, recurrence rate, preservation of function, patient expectations, and potential adverse events should be considered.

Surgical

The choice of surgical procedure depends on the histologic type, size, and location of the lesion. Patient preferences can also play a factor in surgical decisions due to cosmetic reasons, as well as the consideration of comorbidities and patient risk factors, such as anticoagulation. Local excisional procedures, such as electrodesiccation and curettage or cryotherapy, can be used for low-risk lesions, while surgical excision is indicated for lesions that are not low risk. Mohs surgery is an excisional procedure that uses microscopic guidance to achieve greater precision and sparing of normal tissue. In patients who meet criteria for Mohs surgery, 5-year cure rates for basal cell cancer range from 98% to 99%,[5,] making Mohs surgery the preferred procedure for those who qualify.

Radiotherapy

Radiotherapy is indicated for certain NMSCs not amenable to surgery. In some cases, this is due to the location of the lesion on the eyelid, nose, or other structures that make surgery more difficult and which may be expected to have a less desirable cosmetic outcome. In other cases,

surgery may be relatively contraindicated due to clinical factors, such as bleeding risk or advanced age. In elderly patients with a relatively large tumor that would require extensive excision, the benefit/risk ratio for radiotherapy may be considered favorable. The 5-year control rates for radiotherapy range from 80% to 92%, which is lower than that of surgical excision.[5,] A randomized controlled trial by Avril et al (1997) reported that radiotherapy for basal cell carcinoma resulted in greater numbers of persistent and recurrent lesions compared with surgical excision.[6,]

When radiotherapy is used for NMSC, the primary modality is external-beam radiotherapy. A number of different brachytherapy techniques have also been developed, including low-dose rate systems, iridium-based systems, and high-dose rate systems.[5,]

Electronic Brachytherapy

Electronic brachytherapy is a form of radiotherapy delivered locally, using a miniaturized electronic X-ray source rather than a radionuclide-based source. A pliable mold, constructed of silicone or polymethyl-methacrylate, is fitted to the tumor surface. This mold allows treatment to be delivered to nonflat surfaces such as the nose or ear. A radioactive source is then inserted into the mold to deliver a uniform radiation dosage directly to the lesion.[5,] Multiple treatment sessions within a short time period (typically within a month) are required.

This technique is feasible for well-circumscribed, superficial tumors because it focuses a uniform dose of X-ray source radiation on the lesion with the aid of a shielded surface application. Advantages of this treatment modality compared with standard radiotherapy include a shorter treatment schedule, avoidance of a surgical procedure and hospital stay, less severe side effects because the focused radiation spares healthy tissue and organs, and the avoidance of radioisotopes.[5,]

REGULATORY STATUS

Electronic brachytherapy systems for the treatment of NMSCs are designed to deliver high-dose rate brachytherapy to treat skin surface lesions. This technique focuses a uniform dose of X-ray source radiation to the lesion with the aid of a shielded surface application. The Superficial X-Ray Radiation Therapy SRT-100 Vision™ System (Sensus Healthcare), Esteya® Electronic Brachytherapy System (Nucletron BV), and the Xoft® Axxent® Electronic Brachytherapy System (iCAD) are systems that have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process.

U.S. Food and Drug Administration product code: JAD.

POLICY

Electronic brachytherapy for the treatment of nonmelanoma skin cancer is considered **experimental / investigational**.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through May 18, 2023.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

ELECTRONIC BRACHYTHERAPY FOR NONMELANOMA SKIN CANCER

Clinical Context and Therapy Purpose

The purpose of electronic brachytherapy in individuals who have nonmelanoma skin cancer (NMSC) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with NMSC. Nonmelanoma skin cancer refers to squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). There are other less common types of skin cancer, such as T-cell lymphoma or Merkel cell tumor, which may have specific treatment options that differ from SCC and BCC and may need to be considered on an individual basis.

Interventions
The therapy being considered is electronic brachytherapy. Electronic brachytherapy is a form of radiotherapy delivered locally, using a miniaturized electronic X-ray source rather than a radionuclide-based source. Multiple treatment sessions within a short time period (typically within a month) are required.

Comparators
The following therapies are currently being used: surgery (excision or Mohs surgery), external-beam radiotherapy (EBRT), and standard brachytherapy.

The diagnosis of NMSC involves a detailed review of medical history, a clinical exam, and a skin biopsy. Information from the diagnostic process can assess the risk of recurrence, which informs the choice of treatment. Location and size of the skin cancer are also factors in choosing the treatment strategy. Brachytherapy is considered when lesions are located on anatomic curves or are near critical organs.

Outcomes
The general outcomes of interest are survival, recurrence rates, and treatment-related morbidity. Follow-up to adequately detect NMSC recurrence should be at least 5 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews
Lee et al (2019) published a meta-analysis of 58 studies including 21,371 patients treated with conventional surgical excision (24 studies), Mohs micrographic surgery (MMS; 13 studies), EBRT (19 studies), or high-dose-rate brachytherapy (7 studies) for indolent BCC and SCC of the skin.[7,] "Good" cosmesis was reported in 81% (95% confidence interval [CI], 70.6% to 89.6%), 74.6% (95% CI, 63% to 84.6%), and 97.6% (95% CI, 91.3% to 100%) of patients treated with

conventional excision, EBRT, and brachytherapy, respectively. This was comparable to the 96% "good" cosmesis grade outcome reported in 1 MMS study. The 5-year local recurrence rate for brachytherapy was 2.5% (95% CI, 0.8% to 5.1%), which was comparable to both MMS (1.8%; 95% CI, 1.1% to 2.7%) and conventional excision (2.1%; 95% CI, 1.0% to 3.5%). The authors concluded that interpretation of results may be limited by selection bias and subjective and heterogeneous cosmesis grading systems, warranting further prospective, comparative studies.

Delishaj et al (2016) published a systematic review of studies on high-dose rate brachytherapy, including electronic brachytherapy, for the treatment of NMSC.[8,] A literature review conducted through May 2019 identified 10 case series with sample sizes of 20 patients or more that reported on nonoverlapping patients. Findings were reported for 1870 patients (N=1870 lesions). Most lesions (65%) were BCC and the second largest group (35%) was SCC. Reviewers did not pool study findings, reporting that the rates of local control ranged from 83% to 100%. After a median follow-up ranging from 9 months to 10 years, recurrence rates ranged from 0% to 17%. Seven of the 10 studies reported recurrence rates of less than 5%, 2 had recurrence rates of 8% to 9%, and 1 study had a recurrence rate of 17%. The 2 studies with recurrence rates in the 8% to 9% range used Leipzig applicators and the study with a 17% recurrence rate used high-dose rate brachytherapy with surface applicators or custom-made surface molds.

Prospective Cohort Study

Patel et al (2017)[9,] published preliminary results from a multi-center prospective matched pair cohort study (NCT03024866) comparing clinical outcomes of NMSC treated with electronic brachytherapy or MMS. Patients from 4 treatment centers who had already received treatment for NMSC with electronic brachytherapy and met eligibility criteria were invited to participate. A retrospective chart review was used to individually match patients with patients who had received MMS for NMSC based on patient age (±15 years), lesion size, type and location, and treatment dates. All MMS-treated subjects treated in the same time-frame were considered for matching and the final pair was selected based on the closest match of demographics and lesion characteristics. A total of 369 patients were included for study representing 208 matched lesion pairs. Additional eligibility criteria included:

- completion of electronic brachytherapy or MMS for NMSC ≥3 years prior
- age >40 yrs
- diagnosis of SCC or BCC
- cancer stage 0 to 2

Exclusion criteria included:

- target area adjacent to burn scar
- surgical resection of the cancer prior to electronic brachytherapy
- presence of actinic keratosis
- known metastatic disease

Patients were evaluated for follow-up at 2.3 to 5.0 years post-treatment. Treatment with electronic brachytherapy was performed with a miniature, high dose rate electronic X-ray source using standard surface applicators. A dose of 40.0 Gy in 8 fractions (5 Gy twice weekly) was used to delivered to a depth of 2 to 3 mm but in some cases a customized dose, depth, or schedule was used. Mohs micrographic surgery was performed by clinicians according to guidelines of the American College of Mohs Surgery. Matching of patients on lesion characteristics was based on the histopathology of BCC or SCC, cancer staging (Stage 0, Stage 1, Stage 2), size (≤1 cm, >1

cm and ≤2 cm, >2 cm and ≤3 cm), and location (head, ear, eyelid, face/neck, lip, scalp, nose, torso, lower extremity, upper extremity). The mean follow-up length was 3.3 years for the electronic brachytherapy group and 3.5 years for the MMS group. The primary outcome was absence of NMSC recurrence at follow-up. Secondary outcomes included late toxicities, cosmetic outcomes, and patient satisfaction with treatment. All patients completed all evaluations.

The main characteristics and results are summarized in Table 1.

Table 1. Prospective Cohort Studies of Electronic Brachytherapy for Nonmelanoma Skin Cancer

Study	Population	N	FU	Treatment	Outcomes			
Patel et al (2017)[9,]	Patients receiving EBT for NMSC	188		EBT				
	Lesions receiving EBT for NMSC (number of lesions, %)	208	Mean 3.3 ± 0.4 y (range 2.6 to 4.3)	EBT	Absence of Local Recurrence at Follow-Up (number of lesions, %, 95% CI)	Cosmesis Grade at Follow-Up (number of lesions, %, 95% CI)[a]	Long-term Toxicities Present at Follow-Up (number of lesions, %)	Results of Patient Satisfaction Questionnaire at Follow-Up (mean ± SD; median, [10-60])[b]
	• Lesions with BCC (113, 54.3%) • Lesions with SCC (95, 45.7%)	208	Mean 3.3 ± 0.4 y (range 3.2; 2.6 to 4.3)	EBT	207 (99.5%, 97.4 to 100%)	Clinician Cosmesis Grade • Excellent/Good (203, 97.6%, 94.5 to 99.2%) • Excellent (133, 63.9%) • Good (70, 33.7%) • Fair (1, 0.5%) • Poor (4, 1.9%) Subject Cosmesis Grade • Excellent (140, 67.3%) • Good (48, 23.1%) • Fair (15,	No changes, relatively invisible scar (138, 66.7%) Late toxicities: • Hypopigmentation (124, 59.6%) • Hyperpigmentation (11, 5.3%) • Erythematous scar (6, 2.9%) • Telangiectasia (65, 31.4%) • Hair loss (8, 3.9%) • Fibrosis (3, 1.4%) • Atrophy (12, 5.8%) • Loss of subcutaneous tissue (7, 3.4%)	54.0 ± 9.0; 58.0 Individual Questions • Treatments were convenient (4.3 ± 1.1) • Satisfied with how well treatment worked (4.5 ± 1.1) • Satisfied with appearance of the treated area (4.4 ± 1.0) • If another cancer, would use

Study	Population	N	FU	Treatment	Outcomes			
						7.2%) • Poor (5, 2.4%)	• Hypertrophy (excessive fibrosis) or keloid (0, 0%) • Poor healing, ulceration, erosion (4, 1.9%)	same treatment (4.1 ± 1.4) • Have not had any skin problems with treated area (4.5 ± 1.2) • Since treatment, frustrated about appearance of treated site (4.5 ± 1.1) • Since treatment, embarrassed about appearance of treated site (4.6 ± 0.9) • Since treatment, depressed about appearance of treated site (4.5 ± 1.1) • Treatment prevented me from participating in daily activities (4.6 ± 0.9) • Treatment made it hard to work or do what I enjoy (4.7 ± 0.7) • Would recommend treatment to others (4.4

Study	Population	N	FU	Treatment	Outcomes			
								± 1.3) • Always followed instructions related to care of treated area (4.9 ± 0.4)
	Patients receiving MMS for NMSC	181	---	MMS	Outcomes			
	Lesions receiving MMS for NMSC (number of lesions, %)	208	Mean 3.5 ± 0.5 y (range 2.3 to 5.0)	MMS	Absence of Local Recurrence at Follow-Up (Number of lesions, %, 95% CI)	Cosmesis Grade at Follow-Up (Number of lesions, %, 95% CI)[a]	Long-term Toxicities Present at Follow-Up (Number of lesions, %)	Results of Patient Satisfaction Questionnaire at Follow-Up (mean ± SD; median, [10 to 60])[b]
	• Lesions with BCC (113, 54.3%) • Lesions with SCC (95, 45.7%)	208	Mean 3.5 ± 0.5 y (range 2.3 to 5.0)	MMS	208 (100%, 98.2 to 100%)	Clinician Cosmesis Grade • Excellent/Good (199, 95.7%, 92.0 to 98.0%) • Excellent (142, 68.3%) • Good (57, 27.4%) • Fair (9, 4.3%) • Poor (0, 0.0%) Subject Cosmesis Grade • Excellent (148, 71.1%) • Good (50, 24.0%) • Fair (10, 4.8%)	No changes, relatively invisible scar (143, 68.8%) Late toxicities: • Hypopigmentation (109, 52.4%) • Hyperpigmentation (4, 1.9%) • Erythematous scar (15, 7.2%) • Telangiectasia (23, 11.1%) • Hair loss (7, 3.4%) • Fibrosis (2, 1%) • Atrophy (9, 4.3%) • Loss of subcutaneous tissue (6, 2.9%) • Hypertrophy (excessive	56.0 ± 5.3; 59.0 • Treatments were convenient (4.7 ± 0.6) • Satisfied with how well treatment worked (4.8 ± 0.5) • Satisfied with appearance of the treated area (4.6 ± 0.7) • If another cancer, would use same treatment (4.6 ± 0.7) • Have not

Study	Population	N	FU	Treatment	Outcomes			
						• Poor (0, 0.0%)	fibrosis) or keloid (3, 1.4%) • Poor healing, ulceration, erosion (0, 0.0%)	had any skin problems with treated area (4.7 ± 0.6) • Since treatment, frustrated about appearance of treated site (4.6 ± 1.0) • Since treatment, embarrassed about appearance of treated site (4.7 ± 0.7) • Since treatment, depressed about appearance of treated site (4.6 ± 0.8) • Treatment prevented me from participating in daily activities (4.6 ± 0.9) • Treatment made it hard to work or do what I enjoy (4.6 ± 0.8) • Would recommend treatment to others (4.7 ± 0.7) • Always followed instructions

Study	Population	N	FU	Treatment	Outcomes			
								related to care of treated area (4.7 ± 0.5)
Kuo et al (2022)[10],	Age ≥60y with AJCC T1N0M0 BCC or SCC	34	12 weeks	EBT	Cosmesis grade at 12 weeks, n (%)	Quality of life, mean (SD)	Adverse events	--
					Clinician • Good: 31 (96.9) • Fair: 1 (3.1) • Bad: 0 • ND: 2 Patient • Good: 31 (93.9) • Fair: 2 (6.1) • Bad: 0 • ND: 1	Skindex-16, baseline (N=34) • Symptoms: 7.4 (17.7) • Emotions: 19.7 (24.0) • Functioning: 4.4 (10.5) • Total: 10.5 (14.9) Skindex-16, 12 weeks (n=33) • Symptoms: 1.6 (3.7) • Emotions: 3.1 (6.0), p≤.006 vs baseline • Functioning: 1.5 (7.0) • Total: 2.1 (4.6), p≤.017 vs baseline Skin Cancer Index, baseline (N=34) • Emotional: 77.7 (22.2) • Social: 90.1 (19..1) • Appearance: 67.4 (33.1)	• Most frequent: radiation dermatitis, skin pain, pruritus • Grade 3 adverse events reported in week 3 of treatment (painful skin, 6.6%) and 2 weeks after treatment (radiation dermatitis, 42.4%)	

Study	Population	N	FU	Treatment	Outcomes			
						• Total: 78.4 (21.9) Skin Cancer Index, 12 weeks (n=33) • Emotional: 86.3 (15.7) • Social: 92.3 (13.4) • Appearance: 87.6 (20.3), p≤.006 vs baseline • Total: 88.7 (13.3)		

AJCC: American Joint Committee on Cancer; BCC: basal cell carcinoma; CI: confidence interval; EBT: electronic brachytherapy; FU : follow-up; MMS: Mohs micrographic surgery; ND: no data; NMSC: nonmelanoma skin cancer; SCC: squamous cell carcinoma; SD: standard deviation.
[a] Standardized scale adapted from Cox et al (1995).[11,]
[b] A score of 5 represents the maximum positive or favorable response to each question.

No statistically significant difference was found between electronic brachytherapy (97.6%) and MMS (95.7%) groups for local recurrence absence (p=1.000). However, 1 recurrence was reported in the EBT group at 1 year post-treatment. No recurrences occurred in the MMS group. No statistically significant differences were noted for secondary endpoints of cosmesis (p=.277) and patient satisfaction with both groups demonstrating predominantly excellent cosmesis grades and high patient satisfaction scores. Late toxicities appeared at similar rates with telangiectiasa being reported slightly more in the electronic brachytherapy versus MMS group (31.4% vs. 11.1%).

A summary of study relevance limitations is provided in Table 2.

Table 2. Study Relevance Limitations

Study (year)	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Patel et al (2017)[9,]	2. Rationale for inclusion and exclusion criteria unclear	2. Version used unclear		6. Clinically significant difference not supported	1. Not sufficient duration for benefit
Kuo et al (2022)[10,]		2. Version used unclear	5. No comparator	1. Recurrence rates not reported	1. Not sufficient duration for benefit

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

A summary of study design and conduct limitations is provided in Table 3.

Table 3. Study Design and Conduct Limitations

Study (year)	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Patel et al (2017)[9,]	3. Allocation concealment unclear in matching procedure	3. Outcome assessed by treating physician	2,3. Evidence of selective reporting and publication	5. Unclear whether patients with metastatic disease should be excluded or whether age exclusion is clinically relevant	1,2. Power calculations not reported for primary outcome	
Kuo et al (2022)[10,]	1,2. Open-label single-arm trial	1,2. Open-label 4. Unknown if outcome assessed by treating physician				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Case Series

Evidence also includes uncontrolled studies. The main characteristics and results of published case series are summarized in Table 4.

Table 4. Case Series of Electronic Brachytherapy for Nonmelanoma Skin Cancer

Study	Population	N	MFU, mo	Treatment	Outcomes	
					Recurrence	Toxicity, %
Doggett et al (2023)[12,]	Basal or squamous cell carcinoma with ≥5y follow-up	180	90	• 40 Gy in 8 twice-weekly fractions	1.1%	• Hypopigmentation grade 1: 65.9% • Telangectasia grade 1: 22.5% • Scar grade 1: 1.1% • Hyperpigmentation grade 1: 1.1% • Induration grade 2: 0.5%
Pellizzon et al (2020)[13,]	Basal or squamous cell carcinoma	71	42.8	• Leipzig applicator • Total dose: 28 to 55 Gy in 7 to 22 fractions	6.9%	Acute: • Grade 1 to 2=100 • Grade 3= 8.9 Late: • Grade 3=3.9 • Grade 4=0
Paravati et al (2015)[14,]	Basal, squamous, or basosquamous cell carcinoma	127	16.1	• Axxent Xoft system • Total dose: 40 Gy in 8 fractions delivered 2 times weekly	1.2%[c](2/154)	Acute: • Grade 0 to 1=53 • Grade 2=34.4 • Grade 3=13 Late: • Grade 0 to 1=94 • Grade 2=6
Delishaj et al (2015)[15,]	Nonmelanoma skin cancer	39	12	• Valencia applicator • Total dose: 40 Gy in 8 fractions	0%	Acute: • Grade 1=58 • Grade 2=5 Late: • Grade 1=19 • Grade 2=2
Tormo et al (2014)[16,]	Basal cell carcinoma	32	47	• Valencia applicator • Total dose: 42 Gy in 6 to 7 fractions	3.1%	• Grade 1=NR • Grade 2=0 • Grade 3=0

Study	Population	N	MFU, mo	Treatment	Outcomes	
Bhatnagar et al (2013)[1,];Bhatnagar & Loper (2010)[17,,a]	Nonmelanoma skin cancer	122	10.0	• Axxent Xoft system • Total dose: 40 Gy in 8 fractions delivered twice weekly	0%	• Grade 1=11 • Grade 2=13 • Grade 3=0
Gauden et al (2013)[18,]	Small nonmelanoma skin cancers	200	66[b]	• Leipzig applicator • Total dose: 36 Gy in 12 fractions delivered daily	2%[c](4/236)	• Grade 1=71 • Grade 2=34 • Grade 3=0
Giux et al (2000)[19,]	Basal or squamous cell carcinoma	136	60	• Brock applicator • Total dose: 60 to 65 Gy in 33 to 36 fractions	2.2%	NR ("no severe complications")

MFU: mean follow-up; NR: not reported.
[a] Overlapping case series; results from larger, more recent publication reported.
[b] Median.
[c] Calculated based on number lesions not patients.

The largest series was published by Gauden et al (2013) and included 200 patients with 236 lesions (121 basal cell, 115 squamous cell).[18,] Brachytherapy was the primary treatment modality in 69% of the lesions, while in the remaining 31% (74/236) brachytherapy was a follow-up treatment to surgery when there were positive margins. Outcomes included treatment efficacy, as measured by local recurrence rate, skin toxicity measured using Radiation Therapy Oncologic Group criteria, and cosmetic outcome using the Radiation Therapy Oncologic Group Cosmesis Scale. After a median follow-up of 66 months, there were recurrences in 2% (4/236) of treated lesions. Cosmetic outcome was judged to be excellent or good in 88% (208/236) of treated lesions. Grade 1 skin toxicity was common (71% of treated lesions); grade 2 toxicity was less common (34%); and no instances of grade 3 or higher toxicities were noted. Late hypopigmentation of treated skin was reported in 5.5% (13/236) of treated lesions.

Bhatnager (2013) published a case series using a commercially available device (Axxent eBx System).[1,] The series included 122 patients with 171 nonmelanoma skin lesions. Most patients

had either BCC (53%) or SCC (41%); 10 (5.8%) patients had other types of cancer. Outcome measures included recurrence rates, adverse events using version 3.0 of the Common Terminology Criteria for Adverse Events, and cosmetic results using a standardized Cosmesis Scale. After a mean 10-month follow-up, there were no local recurrences. Dermatitis and pruritus were common early adverse events, occurring in 83% and 18% of the treated lesions, respectively. Skin hypopigmentation was the most common late adverse event, occurring in 10.9% of lesions at 1 year. Other late complications included rash (6.5%), alopecia (2.2%), and dry desquamation (2.2%). All patients had their cosmetic outcomes rated as good or excellent.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Dermatology

In 2018, the American Academy of Dermatology published guidelines on the management of basal cell carcinoma [4,] and the management of squamous cell carcinoma.[20,] Electronic brachytherapy was rated as a C recommendation, with a level of evidence of II and III. By comparison, surgery, cryosurgery, topical therapies, and photodynamic therapies are rated as A and B recommendations.

American Brachytherapy Society

The American Brachytherapy Society issued a consensus statement on electronic brachytherapy following a literature review focused on trials, prospective studies, multi-institutional series, and single institution reports addressing clinical outcomes and toxicities.[21,] Due to a lack of comparative data to traditional treatments and limited long-term follow-up, prospective studies with a larger number of patients undergoing electronic brachytherapy for nonmelanoma skin cancer are recommended. At this time, the statement recommends that treatment with electronic brachytherapy in this patient population should be performed in the context of a clinical registry or trial. This recommendation was reaffirmed in a 2020 American Brachytherapy Society consensus statement on skin brachytherapy.[22,]

American Society for Radiation Oncology

The American Society for Radiation Oncology (ASTRO) issued clinical practice guidelines regarding definitive and postoperative radiation therapy for basal and squamous cell cancers of the skin.[23,] Key questions were addressed by a systematic literature review and recommendations were developed via consensus with a modified Delphi approach. Consensus recommendations for specific dose-fractionation schemes are detailed for the definitive and post-operative settings. The guideline also states that appropriate use of any of the 4 major radiation modalities, including electronically-generated low energy sources such as electronic brachytherapy, result in similar local control and cosmetic outcomes. Therefore, "the decision of which modality and

fractionation scheme to use should be based on both tumor characteristics (e.g., shape, contour, depth, and location) and normal tissue considerations."

National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines on basal cell carcinoma (v.1.2023) [24,]and squamous cell skin cancer (v.1.2023)[25,] both contain the following statement on brachytherapy: "There is insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Ongoing Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02131805	A Multicenter Pilot Study of Electronic Skin Surface Brachytherapy for Cutaneous Basal Cell and Squamous Cell Carcinoma	36	May 2024
Unpublished			
NCT01016899[a]	Xoft Electronic Brachytherapy Clinical Protocol for the Primary Treatment of Non-Melanoma Skin Cancer	100	Aug 2013 (completed)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
0394T	High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed

REVISIONS	
09-14-2017	Policy added to the bcbsks.com web site on 08-15-2017 with an effective date of 09-14-2017.
09-12-2018	Updated Description section.
	In Policy section: ▪ Removed "(see Policy Guidelines)" to read "Electronic brachytherapy for the treatment of nonmelanoma skin cancer is considered experimental / investigational." ▪ Policy Guidelines removed.
	Updated Rationale section.
	Updated References section.
08-28-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.
04-19-2021	Updated Description section.
	Updated Rationale section.
	Updated References section.
12-16-2021	Updated Description section.
	Updated Rationale section.
	Updated References section.
09-13-2022	Updated Description Section
	Updated Rationale Section
	Updated References Section
09-12-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Diagnoses Box
	Updated References Section

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