

## Medical Policy



### Title: Electronic Brachytherapy for Nonmelanoma Skin Cancer

#### Professional

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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. 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 policy 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 in the United States, affecting between 1 and 3 million people per year<sup>1,2</sup> and increasing at a rate of 3% to 8% per year.<sup>2</sup> Other types (eg, T-cell lymphoma, Merkel cell tumor, basosquamous carcinoma, Kaposi sarcoma) are much less common. The primary risk factor for nonmelanoma skin cancer is sun exposure, with additional risk factors such as toxic exposures, other ionizing radiation exposure, and immunosuppression playing smaller roles.<sup>2</sup> 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 nonmelanoma skin cancer is surgical. If surgery is not feasible or preferred, cryosurgery, topical therapy, or radiotherapy can be considered, though the cure rate may be lower.<sup>3</sup> 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 and size and location of the lesion. Patient preferences may also be part of the decision-making process, with consideration of comorbidities, patient risk factors (eg, anticoagulation), and cosmetic outcomes. 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 a type of 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%,<sup>4</sup> making Mohs surgery the preferred procedure for those who qualify.

### Radiotherapy

Radiotherapy is indicated for certain nonmelanoma skin cancers 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 are range from 80% to 92%, which is lower than for surgical excision.<sup>4</sup> A 1997 randomized controlled trial published reported that radiotherapy for basal cell carcinoma resulted in greater numbers of persistent and recurrent lesions compared with surgical excision.<sup>5</sup>

When radiotherapy is used for nonmelanoma skin cancer, the primary modality is external beam radiation. A number of different brachytherapy techniques have also been

developed, including low-dose rate systems, iridium-based systems, and high-dose rate systems.<sup>4</sup>

*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 is constructed of silicone or polymethyl-methacrylate and 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 contact the tumor and deliver a uniform radiation dosage directly to the lesion.<sup>4</sup> 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. Potential 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.

### **REGULATORY STATUS**

Electronic brachytherapy systems for the treatment of nonmelanoma skin cancers 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 Esteya® Electronic Brachytherapy System (Nucletron BV) and the Xofigo® Axxent® Electronic Brachytherapy System (iCAD Inc.) are 2 systems that have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. FDA product code: JAD.

### **POLICY**

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

### **RATIONALE**

This evidence review was performed through May 7, 2018.

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 one 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 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.

## **Electronic Brachytherapy for Nonmelanoma Skin Cancer**

### Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does the use of electronic brachytherapy improve the net health outcome in patients with nonmelanoma skin cancer?

The following PICOTS were used to select literature to inform this review.

### Patients

The relevant population of interest is patients with nonmelanoma skin cancer. Nonmelanoma skin cancer refers to squamous cell carcinoma and basal cell carcinoma. 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 basal and squamous cell carcinomas and may need to be considered on an individual basis.

### Interventions

The therapy being considered is electronic brachytherapy.

### Comparators

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

The diagnosis of nonmelanoma skin cancer 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.

### Timing

Follow-up to adequately detect nonmelanoma skin cancer recurrence should be at least 5 years.

### Setting

Electronic brachytherapy is usually administered in a hospital or free-standing facility.

### Systematic Reviews

Delishaj et al (2016) published a systematic review of studies on high-dose rate brachytherapy, including electronic brachytherapy, for the treatment of nonmelanoma skin cancer.<sup>6</sup> A literature review conducted through May 2016 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 basal cell carcinoma and the second largest group (35%) was squamous cell carcinoma. Reviewers did not pool study findings, reporting that the rates of local control ranged from 83% to 100%. After 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.

### Case Series

Evidence consists of uncontrolled studies. The main characteristics and results of published case series are summarized in Table 1.

**Table 1. Case Series of Electronic Brachytherapy for Nonmelanoma Skin Cancer**

Study	Population	N	MFU, mo	Treatment	Outcomes	
					Recurrence	Toxicity, %
Paravati et al (2015) <sup>7</sup>	Basal, squamous, or basosquamous cell carcinoma	127	16.1	<ul style="list-style-type: none"> <li>• Axxent Xoft system</li> <li>• Total dose: 40 Gy in 8 fractions delivered 2 times weekly</li> </ul>	1.2% <sup>c</sup> (2/154)	Acute: <ul style="list-style-type: none"> <li>• Grade 0-1=53</li> <li>• Grade 2=34.4</li> <li>• Grade 3=13</li> </ul> Late: <ul style="list-style-type: none"> <li>• Grade 0-1=94</li> <li>• Grade 2=6</li> </ul>
Delishaj et al (2015) <sup>8</sup>	Nonmelanoma skin cancer	39	12	<ul style="list-style-type: none"> <li>• Valencia applicator</li> <li>• Total dose: 40 Gy in 8 fractions</li> </ul>	0%	Acute: <ul style="list-style-type: none"> <li>• Grade 1=58</li> <li>• Grade 2=5</li> </ul> Late: <ul style="list-style-type: none"> <li>• Grade 1=19</li> <li>• Grade 2=2</li> </ul>
Tormo et al (2014) <sup>9</sup>	Basal cell carcinoma	32	47	<ul style="list-style-type: none"> <li>• Valencia applicator</li> <li>• Total dose: 42 Gy in 6-7 fractions</li> </ul>	3.1%	<ul style="list-style-type: none"> <li>• Grade 1=NR</li> <li>• Grade 2=0</li> <li>• Grade 3=0</li> </ul>
Bhatnagar (2013) <sup>1</sup> ; Bhatnagar & Loper (2010) <sup>10,a</sup>	Nonmelanoma skin cancer	122	10.0	<ul style="list-style-type: none"> <li>• Axxent Xoft system</li> <li>• Total dose: 40 Gy in 8 fractions delivered twice weekly</li> </ul>	0%	<ul style="list-style-type: none"> <li>• Grade 1=11</li> <li>• Grade 2=13</li> <li>• Grade 3=0</li> </ul>
Gauden et al (2013) <sup>11</sup>	Small nonmelanoma skin cancers	200	66 <sup>b</sup>	<ul style="list-style-type: none"> <li>• Leipzig applicator</li> <li>• Total dose: 36 Gy in 12 fractions delivered daily</li> </ul>	2% <sup>c</sup> (4/236)	<ul style="list-style-type: none"> <li>• Grade 1=71</li> <li>• Grade 2=34</li> <li>• Grade 3=0</li> </ul>
Giux et al (2000) <sup>12</sup>	Basal or squamous cell carcinoma	136	60	<ul style="list-style-type: none"> <li>• Brock applicator</li> <li>• Total dose: 60-65 Gy in 33-36 fractions</li> </ul>	2.2%	NR ("no severe complications")

Gy: gray; MFU: mean follow-up; NR: not reported. <sup>a</sup> Overlapping case series; results from larger, more recent publication reported.

<sup>b</sup> Median. <sup>c</sup> 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).<sup>11</sup> 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).<sup>1</sup> The series included 122 patients with 171 nonmelanoma skin lesions. Most patients had either basal cell carcinoma (53%) or squamous cell carcinoma (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.

### **SUMMARY OF EVIDENCE**

For individuals who have nonmelanoma skin cancer who receive electronic brachytherapy, the evidence includes a systematic review and case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. No controlled trials were identified that compared electronic brachytherapy with alternative treatment options. A 2016 systematic review of case series found local control rates ranging from 83% to 100% and recurrence rates ranging from 0% to 17%. In most studies, the recurrence rate was less than 5%. In the absence of controlled studies, conclusions cannot be drawn about the efficacy and safety of electronic brachytherapy compared with other treatments for nonmelanoma skin cancer. Controlled trials are needed in defined populations that compare electronic brachytherapy with alternatives, either other forms of radiotherapy or surgical approaches. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **PRACTICE GUIDELINES AND POSITION STATEMENTS**

#### National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on basal cell carcinoma (v.1.2018)<sup>13</sup> and squamous cell skin cancer (v.1. 2019)<sup>14</sup> both contain the following statement on electronic brachytherapy: "There is insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy."

#### American Academy of Dermatology

The American Academy of Dermatology (2018) published guidelines on the management of basal cell carcinoma<sup>3</sup> and the management of squamous cell carcinoma.<sup>15</sup> Electronic brachytherapy was rated as a C recommendation, with the level of evidence of II and III. By comparison, surgery,

cryosurgery, topical therapies, and photodynamic therapies are rated as A and B recommendations.

### U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

### ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 2.

**Table 2.** Summary of Key Ongoing Trials

Nct No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT03024866 <sup>a</sup>	Electronic Brachytherapy: A Multi-Center Retrospective-Prospective Matched Pairs Cohort Study to Assess Long Term Clinical Outcomes of Nonmelanoma Skin Cancer Patients Treated with eBx Compared to Nonmelanoma Skin Cancer Patients Treated with Mohs Surgery	500	Jan 2018 (ongoing)
NCT01016899 <sup>a</sup>	Xoft Electronic Brachytherapy Clinical Protocol for the Primary Treatment of Non-Melanoma Skin Cancer	100	Feb 2016 (ongoing)
NCT02131805	Electronic Skin Surface Brachytherapy for Cutaneous Basal Cell and Squamous Cell Carcinoma	26	May 2018

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or co-sponsored trial.

### CODING

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. 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.**

#### CPT/HCPCS

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

#### Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

### 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: <ul style="list-style-type: none"> <li>▪ Removed "(see Policy Guidelines)" to read "Electronic brachytherapy for the treatment of nonmelanoma skin cancer is considered experimental / investigational."</li> <li>▪ Policy Guidelines removed.</li> </ul>
	Updated Rationale section.
	Updated References section.

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