Electronic Brachytherapy for Nonmelanoma Skin Cancer

Policy # 00477
Original Effective Date: 08/19/2015
Current Effective Date: 09/19/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers electronic brachytherapy for the treatment of nonmelanoma skin cancer (Policy Guidelines) to be **investigational.***

Policy Guidelines

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.

Background/Overview

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 and increasing at a rate of 3% to 8% per year. Other types (e.g., 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. Although these cancers rarely fatal, they can impact the quality of life, functional status, and physical appearance.

Treatment

Surgical

Treatment of nonmelanoma skin cancer is primarily surgical, and the choice of surgical procedure depends on the histologic type and 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%, 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 range from 80% to 92%, which is lower than that of surgical excision. A 1997 randomized controlled trial reported that radiotherapy for basal cell carcinoma resulted in greater numbers of persistent and recurrent lesions compared with surgical excision.

When radiotherapy is used for nonmelanoma skin cancer, 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.

Electronic Brachytherapy
Electronic brachytherapy is a form of radiotherapy delivered locally. Available systems for treating nonmelanoma skin cancers are designed to deliver high-dose rate brachytherapy for the treatment of skin surface lesions. 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.

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 contact the tumor and deliver a uniform radiation dosage.

Potential advantages of this treatment modality compared with standard radiotherapy include a shorter treatment schedule and the avoidance of radioisotopes and a dedicated treatment vault.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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 Xoft®‡ Axxent®‡ Electronic Brachytherapy System (iCAD, Nashua, NH) are 2 systems that have been cleared for marketing by the U.S. FDA through the 510(k) process. FDA product code: JAD.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination. In the absence of national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

For this evidence review, relevant outcomes will include measures of efficacy (e.g., response rates, recurrence rates) and measures of safety (e.g., skin toxicity). Cosmetic outcomes are not considered in the

analysis of benefits and risks unless it is demonstrated that a poor cosmetic outcome is associated with deficits in functional status.

ELECTRONIC BRACHYTHERAPY FOR NONMELANOMA SKIN CANCER

The available evidence on electronic brachytherapy for nonmelanoma skin cancer consists of a qualitative systematic review as well as case series. No controlled trials were identified in the published literature that compared outcomes of electronic brachytherapy with alternative treatments.

Systematic Reviews

In 2016, Delishaj et al published a systematic review of studies on high-dose rate brachytherapy, including electronic brachytherapy, for the treatment of nonmelanoma skin cancer. They 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). The majority of 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 between 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

We focused on uncontrolled studies that used a commercially available device for treatment, or that used a technology similar to the commercially available devices. 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 (Year)	Population	N	MFU, mo	Treatment	Outcomes	
					Recurrence	Toxicity
Paravati et al (2015)	Basal, squamous, or basosquamous cell carcinoma	127	16.1	• Axxent Xoft system • 8 fractions delivered 2×/wk • Total dose 40 Gy	1.2% (2/154)	Acute: • Grade 0-1=53% • Grade 2=34.4% • Grade 3=13% Late: • Grade 0-1=94% • Grade 2=6%
Delishaj et al (2015)	Nonmelanoma skin cancer	39	12	• Valencia applicator • 40 Gy in 8 fractions	0%	Acute: • Grade 1=58%

Study (Year)	Population	N	MFU, mo	Treatment	Outcomes	
						• Grade 2=5% Late: • Grade 1=19% • Grade 2=2%
Tormo et al (2014)	Basal cell carcinoma	32	47	• Valencia applicator • 42 Gy in 6-7 fractions	3.1%	• Grade 1=NR • Grade 2=0% • Grade 3=0%
Bhatnagar (2013) (Bhatnagar et al (2010)[a]	Nonmelanoma skin cancer	122	10.0	• Axxent Xoft system • 8 fractions delivered 2×/wk • Total dose 40 Gy	0%	• Grade 1=11% • Grade 2=13% • Grade 3=0%
Gauden et al (2013)	Small nonmelanoma skin cancers	200	66[b]	• Leipzig applicator • 12 fractions delivered daily • Total dose 36 Gy	2%[c] (4/236)	• Grade 1=71% • Grade 2=34% • Grade 3=0%
Giux et al (2000)	Basal or squamous cell carcinoma	136	60	• Brock applicator • Total dose 60-65 Gy in 33-36 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 in 2013 by Gauden et al and included 200 patients with 236 lesions (121 basal cell, 115 squamous cell). Brachytherapy was the primary treatment modality in 69% of the lesions, while in the remaining 31% (74/236) received brachytherapy as 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; Xoft Inc., Sunnyvale, CA). 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 have compared electronic brachytherapy with alternative treatment options. Further, 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, specifically other forms of radiotherapy or surgical approaches. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 08/19/2015
Current Effective Date: 09/19/2018

08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. New Policy
01/01/2016	Coding update
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Added a Policy Guidelines section with a reference to them in the investigational statement. Coverage eligibility unchanged.

Next Scheduled Review Date: 09/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0394T, 77767, 77768
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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