**Electronic Brachytherapy for Nonmelanoma Skin Cancer**

**Summary**

Electronic brachytherapy is a form of radiotherapy that is designed to deliver high-dose rate (HDR) brachytherapy for the treatment of 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.

For individuals who have nonmelanoma skin cancer who receive electronic brachytherapy, the evidence includes 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. The cases series, which usually contained mixed patient populations of basal and squamous cell carcinomas, reported low rates of recurrence, ranging from 0% to 3%, at follow-up periods ranging from 10 to 66 months. Skin toxicity is relatively common, but usually mild. 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.

**Related Policies**

None

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Electronic brachytherapy for the treatment of nonmelanoma skin cancer is considered **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

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\(^1\),\(^2\) 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. 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.\(^2\) Although these cancers rarely cause mortality, they can impact quality of life, functional status, and physical appearance.

Treatment of nonmelanoma skin cancer is primarily surgical.\(^3\) The choice of surgical procedure depends on the histologic type, and size and location of the lesion. Patient characteristics and preferences may also be part of the decision-making process, with consideration of comorbidities, patient risk factors such as anticoagulation and cosmetic outcomes. Local excisional procedures, such as electrodessication 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 are in the range of 98\% to 99\%,\(^4\) making Mohs surgery the preferred procedure for those who qualify.

Radiotherapy is indicated for certain nonmelanoma skin cancers that are 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 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 in the range of 80\% to 92\%, which is lower than for surgical excision.\(^4\) A randomized controlled trial published in 1997 reported that radiotherapy for basal cell carcinoma resulted in greater numbers of persistent and recurrent lesions compared with surgical excision.\(^5\) 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 HDR systems.\(^4\)

Electronic Brachytherapy
Electronic brachytherapy is a form of radiotherapy delivered locally. Available systems for the treatment of nonmelanoma skin cancers are designed to deliver HDR brachytherapy for the treatment of skin surface lesions. This technique is feasible for well-circumscribed, superficial tumors. It focuses a uniform dose of x-ray source radiation to the lesion with the aid of a shielded surface application.

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.\(^4\)
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.¹

**Regulatory Status**

Electronic brachytherapy systems for the treatment of nonmelanoma skin cancers are designed to deliver HDR brachytherapy for the treatment of 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 Inc.) are 2 systems that recently received FDA clearance through the 510(k) process.

The Esteya Electronic Brachytherapy System, approved in 2013, is designed for High Dose Rate (HDR) brachytherapy, treatment of skin surface lesions. The Esteya electronic brachytherapy system is intended to deliver x-ray radiation for surface brachytherapy procedures. Typical applications include treatment for Basal Cell Carcinomas, Squamous Cell Carcinoma, Kaposi’s sarcoma, Merkel Cell Carcinomas, Lentigo Maligna, Lentigo Maligna Melanoma, Keloids and Cutaneous Lymphomas (B and T cell).

Xoft® Axxent® Electronic Brachytherapy System (iCAD Inc.) was approved in 2013. The Axxent Electronic Brachytherapy System is intended to deliver high dose rate X-ray radiation for brachytherapy. The Axxent FlexiShield Mini is intended to shape the beam from a low energy radiation therapy source: up to 50kVp. It is a flexible pad placed over the surface requiring shielding that can used to shape the radiation therapy beam. It can be used on external patient surfaces, as well as internally during Intraoperative Radiation Therapy (IORT).

FDA product code: JAD.

**Rationale**

Assessment of efficacy for a therapeutic intervention involves a determination of whether the intervention improves health outcomes compared with available alternatives. The optimal study design for this purpose is a randomized controlled trial that compares the therapeutic intervention with existing alternative treatments and includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

For the purposes of this evidence review, relevant outcomes will include measures of efficacy (eg, response rates, recurrence rates) and measures of safety (eg, skin toxicity). Cosmetic outcomes will not be considered in the analysis of benefits and risks unless it is demonstrated that a poor cosmetic outcome is associated with deficits in functional status.
Review of Evidence

The available evidence on electronic brachytherapy for nonmelanoma skin cancer consists of case series. No controlled trials were identified in the published literature that compared outcomes of electronic brachytherapy with alternative treatments. The focus of review will be on those case series that use a commercially available device for treatment, or that use a technology similar to the commercially available devices.

The main characteristics and results of these studies are summarized in Table 1. 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) brachytherapy was used as follow-up treatment to surgery when there were positive margins. Outcomes included treatment efficacy, as measured by local recurrence rate, skin toxicity measured according to the Radiation Therapy Oncologic Group (RTOG) criteria, and cosmetic outcome according to the RTOG Cosmesis scale. After a median follow-up of 66 months, there were recurrences in 2% of the treated lesions (4/236). Cosmetic outcome was judged to be excellent or good in 88% of treated lesions (208/236). Grade 1 skin toxicity was common at 71% of treated lesions; grade 2 toxicity was less common in 34%; and there were no grade 3 or higher toxicities noted. Late hypopigmentation of treated skin was reported in 5.5% of treated lesions (13/236).

Bhatnager published a case series using a commercially available device (Axxent eBx System; Xoft Inc., Sunnyvale, CA). There were 122 patients with 171 nonmelanoma skin lesions included. Most patients had either basal cell carcinoma (53%) or squamous cell carcinoma (41%), but there were 10 patients (5.8%) with other types of cancer. Outcome measures included recurrence rates, adverse events using common terminology, and cosmetic results using a standardized cosmesis scale. After a mean duration of follow-up of 10 months, 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.

Other case series have reported similar rates of recurrence (up to 3%). Additional case series identified in the literature are less relevant because they used a different treatment delivery system, treated a more specialized population, and/or had issues such as small sample sizes or short-term follow-up.
Table 1. Case Series of Electronic Brachytherapy for Nonmelanoma Skin Cancer

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Population</th>
<th>N</th>
<th>MFU, mo</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paravati (2015)⁹</td>
<td>Basal, squamous, or basosquamous cell carcinoma</td>
<td>127</td>
<td>16.1</td>
<td>• Axxent Xoft system</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 8 fractions delivered 2×/wk</td>
<td>(2/154)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Total dose 40 Gy</td>
<td></td>
</tr>
<tr>
<td>Delishaj (2015)¹⁰</td>
<td>Nonmelanoma skin cancer</td>
<td>39</td>
<td>12</td>
<td>Valencia applicator</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40 Gy delivered in 8 fractions</td>
<td></td>
</tr>
<tr>
<td>Tormo (2014)⁸</td>
<td>Basal cell carcinoma</td>
<td>32</td>
<td>47</td>
<td>Valencia applicator</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42 Gy delivered in 6-7 fractions</td>
<td></td>
</tr>
<tr>
<td>Bhatnagar (2013)¹</td>
<td>Nonmelanoma skin cancer</td>
<td>122</td>
<td>10.0</td>
<td>• Axxent Xoft system</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 8 fractions delivered 2×/wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Total dose 40 Gy</td>
<td></td>
</tr>
<tr>
<td>Gauden (2013)⁶</td>
<td>Small nonmelanoma skin cancers</td>
<td>200</td>
<td>66⁶</td>
<td>• Leipzig applicator</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 12 fractions delivered daily</td>
<td>(4/236)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Total dose 36 Gy</td>
<td></td>
</tr>
<tr>
<td>Giux (2000)⁷</td>
<td>Basal or squamous cell carcinoma</td>
<td>136</td>
<td>60</td>
<td>• Brock applicator</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Total dose 60-65 Gy in 33-36 fractions</td>
<td>(“no severe complications”)</td>
</tr>
</tbody>
</table>

MFU: mean follow-up; NR: not reported.

⁹ Overlapping case series; results from larger, more recent publication reported.

¹ Median.

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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing NCT01016899a</td>
<td>Xoft Electronic Brachytherapy Clinical Protocol for the Primary Treatment of Non-Melanoma Skin Cancer</td>
<td>100</td>
<td>Feb 2016 (ongoing)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
Summary of Evidence

For individuals who have nonmelanoma skin cancer who receive electronic brachytherapy, the evidence includes 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. The cases series, which usually contained mixed patient populations of basal and squamous cell carcinomas, reported low rates of recurrence, ranging from 0% to 3%, at follow-up periods ranging from 10 to 66 months. Skin toxicity is relatively common, but usually mild. 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.

Supplemental Information

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network guidelines for nonmelanoma skin cancers do not discuss electronic brachytherapy in the following chapters\(^1\):  
- Basal Cell Carcinoma (v.2.2016)  
- Squamous Cell Carcinoma (v.1.2016)  
- Merkel Cell Carcinoma (v.1.2016)  
- Dermatofibrosarcoma (v.1.2016)

As of June 2016, the American Academy of Dermatology was developing guidelines for nonmelanoma skin cancers.\(^2\)

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References


Policy History

<table>
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<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>September 2015</td>
<td>New</td>
<td></td>
</tr>
<tr>
<td>September 2016</td>
<td>Update Policy</td>
<td>Policy created with literature review; references 9-10 added. Policy statement unchanged.</td>
</tr>
</tbody>
</table>

This policy was approved by the FEP Pharmacy and Medical Policy Committee on September 16, 2016 and is effective October 15, 2016.

Signature on File
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