9.03.20 Intraocular Radiation Therapy for Age-Related Macular Degeneration

Summary
Intraocular radiation, including brachytherapy, proton beam therapy (PBT), and stereotactic radiotherapy, are being evaluated to treat choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD).

The evidence for brachytherapy in individuals who have choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) includes a randomized controlled trial (RCT) of brachytherapy plus vascular endothelial growth factor (VEGF) versus VEGF monotherapy, as well as phase 1/2 trials and case series on the use of brachytherapy. Relevant outcomes are change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. The RCT showed that brachytherapy did not attain noninferiority for visual outcomes and was associated with a higher proportion of adverse events. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for proton beam therapy in individuals who have CNV due to AMD includes a randomized, prospective, sham-controlled trial and a pilot study. Relevant outcomes are change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Recruitment into the RCT was halted for ethical concerns and available results did not show statistically significant stabilization of visual acuity. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for stereotactic radiotherapy in individuals who have CNV due to AMD includes an RCT with sham control. Relevant outcomes are change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. The RCT showed a reduction in the number of VEGF treatments at 12- and 24-month intervals, but no significant differences versus controls in changes in visual acuity. The evidence is insufficient to determine the effects of the technology on health outcomes.

FDA REGULATORY STATUS
No devices are specifically approved by the U.S. Food and Drug Administration (FDA) for intraocular radiation. An investigational device exemption was granted by FDA for a phase 3 multicenter trial of the...
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EPI-RAD90™ (now known as Vidion Anti-Neovascular Epimacular Brachytherapy [EMBT] System; NeoVista) to provide data for a device application to FDA. This is a category B procedure.

**POLICY STATEMENT**

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

Intraocular placement of a radiation source (brachytherapy) for the treatment of choroidal neovascularization is considered **investigational**.

Proton beam therapy for the treatment of choroidal neovascularization is considered **investigational**.

Stereotactic radiotherapy for the treatment of choroidal neovascularization is considered **investigational**.

**RATIONALE**

An early search of the literature did identify some older randomized trials using external beam radiotherapy for age-related macular degeneration (AMD)-associated choroidal neovascularization (CNV). Little to no benefit in visual acuity was observed following repeated single treatments of 2 Gy to a total of 12-20 Gy.  

**Brachytherapy**

CABERNET (NCT00454389) is a phase 3 multicenter, randomized controlled trial (RCT) that enrolled 494 subjects with AMD-related wet CNV from 42 sites.  

The safety and efficacy of epiretinal radiotherapy combined with 2 loading injections of ranibizumab (Lucentis®) was compared to ranibizumab monotherapy (2 loading doses and then quarterly). Patients in both arms of the study could receive monthly treatment with ranibizumab as needed. At 24 months, 77% of the patients in the EPI-RAD90 group lost fewer than 15 letters compared with 90% in the control group. This result did not meet the prespecified noninferiority margin. EPI-RAD90 treatment also did not meet the superiority end point, which was the proportion of participants gaining more than 15 letters (16% vs 26% for the ranibizumab group). The most common serious adverse event was cataract surgery (known to be associated with vitrectomy), which occurred in 40% of the EPI-RAD90 group compared with 11% of the ranibizumab monotherapy group. Mild radiation retinopathy occurred in 3% of the patients who received EPI-RAD90 treatment. This study did not support the use of epiretinal radiotherapy.

Twelve- and 24-month results from the multicenter MERITAGE study (NCT00809419) were reported between 2012 and 2014.  

MERITAGE was a phase 1/2 study of EPI-RAD90 for the treatment of subfoveal CNV associated with wet AMD in patients requiring continued antivascular endothelial growth factor (anti-VEGF) therapy to maintain an adequate response. Following a single 24-Gy dose, the 53 patients in the study received retreatment with ranibizumab administered monthly (as needed). In the 12 months before the study, participants received 0.45 injections per month. At the 12-month follow-up, 81% of patients maintained stable vision (loss of <15 letters) with a mean of 3.49 anti-VEGF injections (0.29 per month). Over 24 months, the durability of the application diminished, with 58% of patients maintaining stable vision at a mean of 8.7 anti-VEGF injections (0.72 per month).

Three publications from 2 studies have been reported by Avila et al on epiretinal radiation using the EPI-RAD90 System.  

One report described 12-month safety and visual acuity results from a feasibility study in 34 treatment-naive patients from Turkey, Mexico, and Brazil, recruited between February 2005 and February 2006.  

The second report described 12-month safety and visual acuity results from 24-Gy epiretinal radiation combined with bevacizumab in 34 treatment-naive patients enrolled between June 2006 and April 2007.  

Adverse events related to the device or procedure included subretinal hemorrhage (n=1), retinal tear (n=1), subretinal fibrosis (n=2), epiretinal membrane (n=1), and cataract (n=6/24; 24 patients were phakic at baseline). All occurrences of cataracts were deemed to be related to the
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vitreous surgery. Two- and 3-year results from this trial were published in 2012. All 34 subjects were followed for 24 months; 1 site that enrolled 19 patients agreed to reconsent and follow patients for 3 years. On average, the cohort followed for 36 months received 3.0 bevacizumab injections. Twelve (50%) of the 24 phakic patients developed cataracts, and 4 had phacoemulsification with intraocular lens implantation. Mean change in visual acuity at 36 months was +3.9 letters. Seven (54%) of 13 phakic patients developed cataracts, and 4 had phacoemulsification with intraocular lens implantation. One case of non-proliferative radiation retinopathy was observed at 36 months.

Proton Beam Therapy

In 2012, Park et al reported 12- to 36-month follow-up of a pilot study of ranibizumab combined with proton beam therapy (PBT) for AMD. Six eyes (6 patients) were treated with 4 monthly ranibizumab plus 24-Gy proton beam treatments, followed by ranibizumab if needed. No radiation retinopathy was observed at follow-up.

In 2002, Ciulla et al reported results from a randomized, prospective, sham-controlled, double-masked trial that examined the effect of PBT on subfoveal choroidal neovascular membranes associated with AMD. Thirty-seven subjects were randomly assigned to 16-Gy proton irradiation delivered in 2 fractions 24 hours apart or to sham control treatment. Recruitment was halted at 37 subjects for ethical reasons related to randomization to sham treatment when U.S. Food and Drug Administration approval of Visudyne® (a light-activated drug used with photodynamic therapy) was anticipated. PBT was associated with a trend toward stabilization of visual acuity, but this association was not statistically significant.

Stereotactic Radiotherapy

INTREPID was a randomized, sham-controlled, double-masked trial with 230 patients that assessed the efficacy and safety of stereotactic radiotherapy (SRT) to treat neovascular AMD. The primary outcome measure was the number of ranibizumab injections needed over 52 weeks. Both SRT and sham-control patients received ranibizumab as needed. After 1 year, treatment with 16- or 24-Gy SRT reduced the number of ranibizumab treatments (median of 2 vs 3.5 for sham controls) with no significant differences from controls in changes in visual acuity over the 1-year of follow-up. No safety concerns were identified in the first 12 months.

In 2015, year 2 safety and efficacy results from the INTREPID trial were published. Participants received 16- or 24-Gy SRT or sham SRT and ranibizumab for 12 months, with bevacizumab or ranibizumab thereafter as needed. At year 2, the 16- and 24-Gy arms received fewer as needed bevacizumab (mean, 4.5, p=0.008) or ranibizumab (mean 5.4, p=0.09) treatments compared with sham (mean, 6.6). Changes in mean best-corrected visual acuity were -10.0, -7.5, and -6.7 letters, respectively, with 68%, 75%, and 79% losing fewer than 15 letters, respectively. Differences for visual acuity were not statistically significant. Microvascular abnormalities were detected in 6 control eyes and 29 SRT eyes, of which 18 were attributed to radiation, with only 2 possibly affecting vision. The authors concluded that a single dose of SRT significantly reduced intravitreal injections over 2 years, and that, although radiotherapy can induce microvascular changes, only in 1% of eyes did this seem to affect vision.

Summary of Evidence

The evidence for brachytherapy in individuals who have choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) includes a randomized controlled trial (RCT) of brachytherapy plus vascular endothelial growth factor (VEGF) versus VEGF monotherapy, as well as phase 1/2 trials and case series on the use of brachytherapy. Relevant outcomes are change in disease status, morbidity events, functional outcomes, quality of life, medication use, and treatment-related morbidity. The RCT showed that brachytherapy did not attain noninferiority for visual outcomes and was associated with a
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**SUPPLEMENTAL INFORMATION**

**Ongoing and Unpublished Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td>Ongoing</td>
<td>A Randomised Controlled Trial of Epimacular Brachytherapy Versus Ranibizumab Monotherapy for the Treatment of Subfoveal Choroidal Neovascularisation Associated With Wet Age-related Macular Degeneration in Patients Who Have Commenced Anti-VEGF Therapy</td>
<td>363</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>Unpublished</td>
<td>A Feasibility Study to Evaluate the Safety And Tolerability of the EPI-RAD90™ Ophthalmic System for the Treatment of Subfoveal Choroidal Neovascularization (CNV) in Patients With Age-Related Macular Degeneration (AMD) That Have Failed Primary Anti-VEGF Therapy</td>
<td>20</td>
<td>Jun 2011</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

**Practice Guidelines and Position Statements**

The 2011 guidance from the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) states that current evidence on the efficacy of epiretinal brachytherapy for wet age-related macular degeneration (AMD) is inadequate and limited to small numbers of patients. With regard to safety, vitrectomy has well-recognized complications and there is a possibility of subsequent radiation retinopathy. Therefore this procedure should only be used in the context of research.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.
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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>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2012</td>
<td>New Policy</td>
<td>Policy updated with literature review, references updated and reordered, investigational statement added on proton beam therapy and policy title change to “Intraocular Radiation Therapy” from “Epiretinal Radiation Therapy”</td>
</tr>
<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy was updated with literature review adding references 6, 7, 9 and 10. No change was made to the policy statement. The summary was revised with no change to the intent.</td>
</tr>
<tr>
<td>June 2014</td>
<td>Update Policy</td>
<td>Policy was updated with literature, updating reference 10. No changes to the policy statements.</td>
</tr>
<tr>
<td>June 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 12 and 14 added. Policy statements clarified as to type of radiation therapy used, but intent unchanged.</td>
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<tr>
<td>September 2016</td>
<td>Update Policy</td>
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