Commissioning Policy: Stereotactic Radiotherapy for Neovascular (wet) Age-Related Macular Degeneration (AMD)

Policy decision
Telford and Wrekin Clinical Commissioning Group (CCG) has reviewed the evidence for clinical and cost-effectiveness of stereotactic radiotherapy for neovascular age related macular degeneration.

Until more robust evidence for clinical, safety and cost-effectiveness is available, Telford and Wrekin CCG considers the use of stereotactic radiotherapy in wet age-related macular degeneration to be a LOW PRIORITY intervention that is not routinely commissioned.

Background
Age-related macular degeneration is the term applied to changes, that occur with ageing and without any other obvious cause, in the central area of the retina (macula) in people 50 years of age or older. AMD is the most common cause of blindness in the UK.

A number of treatments are approved by NICE for the management of wet AMD. These include photodynamic therapy, ranibizumab and aflibercept, all of which are funded by the CCG in accordance with NICE guidance.

In March 2004, NICE published Interventional Procedure Guidance (IPG 49) on radiotherapy for age related macular degeneration. NICE concluded that “current evidence shows radiotherapy for age-related macular degeneration to have little efficacy. There are also concerns about its safety. It is suitable for use only within good quality research studies approved by a research ethics committee, specifying the dose of radiation used and with explicit patient consent. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute is not undertaking further investigation at present”. This guidance was considered for reassessment in January 2011. It was concluded that NICE will not be updating this guidance as investigations have suggested that radiotherapy for age-related macular degeneration has been superseded by other techniques.

There has been recent renewed interest in stereotactic radiotherapy after the introduction of a device designed specifically for use in the eye - the iRay System (Oraya Therapy)

Oraya Therapy is a non-invasive treatment for patients with wet AMD. It delivers highly targeted, low energy x-rays to the diseased area of the eye and is intended as a one-time outpatient procedure.

Clinical Evidence
The CCG considered the results of the INTREPID study. INTREPID was undertaken to determine whether stereotactic radiotherapy reduced the frequency of intravitreal ranibizumab injections over 12 months.

The trial recruited 230 patients with chronic, active wet-AMD.

To be included in the study, patients had to meet all of the following inclusion criteria:

• Older than 50 years, with wet AMD diagnosed in the study eye within last 3 years
• Received ≥ 3 ranibizumab or bevacizumab injections within the preceding 52 weeks
• Active disease with continuing need for ranibizumab or bevacizumab intravitreal injections
• The choroidal neovascular lesion had to be < 12 disk areas in size with a greatest linear dimension ≤ 6 mm.
• The distance from the centre of the fovea to the farthest point on the choroidal neovascular lesion perimeter had to be ≤ 3mm.
Participants were randomised to:
- 16-Gray plus ‘when required’ ranibizumab
- 24-Gray plus ‘when required’ ranibizumab
- Sham radiotherapy plus ‘when required’ ranibizumab

All participants received a 0.5mg intravitreal ranibizumab injection at baseline. Thereafter, ranibizumab was administered on a monthly ‘when required’ basis, using defined retreatment criteria.

Results
150 (65%) of the 230 participants received active stereotactic radiotherapy treatment.

Primary outcome measure:
At 12 months both the 16-Gray and 24-Gray stereotactic radiotherapy arms received significantly fewer ranibizumab injections compared with the sham arms: mean numbers of treatments, 2.64, 2.43 and 3.74 respectively (P= 0.013 and P= 0.004 respectively vs sham)\(^1\).

Secondary outcome measures:
The mean change in visual acuity was -0.28 (p = 0.839), +0.4 (p=0.397) and -0.58 letters in the 16 Gray, 24 Gray and sham arms respectively. The difference was not statistically significant\(^1\).

The mean change in subfield thickness was -85.12 (p=0.0054), -68.56 (p=0.0186), and -33.46, respectively\(^1\).

The authors concluded that in patients with previously treated chronic, active choroidal neovascularization resulting from neovascular AMD, the addition of a single dose of 16 Gray or 24 Gray stereotactic radiotherapy resulted in reduced frequency of anti-VEGF retreatment over a 12-month period compared with anti-VEGF monotherapy, and with encouraging structural and functional outcomes. Further studies could consider a more stringent retreatment regimen and would need to be powered to detect a difference in visual acuity and infrequent adverse effects\(^1\). (INTREPID was not designed to show superiority or noninferiority of visual acuity, and a larger phase 3 trial would be needed to draw conclusions on safety and visual efficacy).

Subgroup analysis of INTREPID
The subgroup included participants with lesions ≤ 4 mm in greatest linear dimension and active leakage (macular volume > 7.4 mm\(^2\)). The researchers hypothesised that this group of participants may respond better to stereotactic radiotherapy — radiation is known to preferentially damage proliferating cells, and it is possible that actively proliferating endothelial cells are more likely to leak fluid.

26.1% of the trial population met both of these criteria (i.e. 60 participants – 40 of whom had received active treatment)\(^2\).

In the subgroup the mean reduction in ranibizumab injections over 12 weeks = 2.52 injections (2.08 vs 4.6 = 55% relative reduction). This is highly statistically significant (p=0.0002)\(^2\)

There was also statistically significant improvements in both visual acuity (p=0.0284) and central subfield thickness (p=0.0270)\(^2\).

Patients with lesions > 4mm in greatest linear dimension and macular volume ≤ 7.4mm appeared to have worse outcomes. Eyes in this subgroup had a mean number of ranibizumab retreatments that was very similar to the sham arm (3.50 vs 3.65 injections, not significant)\(^2\).

The authors concluded that the INTREPID study may potentially refine our knowledge of whom best to treat with stereotactic radiotherapy, suggesting that lesions smaller than the 4mm treatment zone do better. It also suggests patients are more likely to respond to stereotactic radiotherapy when they have significant fluid accumulation. These hypotheses, generated from sub-group analysis, need to be tested in a prospective trial\(^2\).
Year 2 Results of the INTREPID Study³
Although the year 1 results of INTREPID were encouraging, they were not sufficient to establish the safety of stereotactic radiotherapy. In particular radiation retinopathy may occur after 1 year, thus necessitating longer surveillance.

Number of ‘when required’ ranibizumab injections at week 104:
Mean number in the sham group = 6.6; Mean number in the combined 16 Gray and 24 Gray group = 4.9. Reduction = 1.7 injections (relative reduction = 26%). This was statistically significant (p=0.009).

Although both the 16 Gray and 24 Gray arms received significantly fewer ranibizumab injections at 12 months, this difference only remained significant at 2 years in the 16 Gray arm (the difference was not significant in the 24 Gray arm).

The change in visual acuity between the combined treatment (i.e. 16 Gray and 24 Gray) and sham arms of the trials were not statistically significant at 2 years.

In the subgroup analysis – i.e. in the 60 eyes with lesions ≤ 4mm and a macular volume >7.4mm³, participants had 45% fewer injections than comparable sham eyes – 3.9 vs 7.1 (i.e. an average of 3.2 fewer injections).

Safety
Microvascular changes in response to radiation occur in about 10% of patients³. Although trials to date have concluded that the changes rarely affect vision, the long term implications not currently understood

Conclusion
Although the evidence provided by INTREPID looks promising, the trial involved small patient numbers and only currently provides data for 2 years post intervention. Longer, larger trials that provide evidence of which patients benefit most from this treatment are required. Trials need to be powered to demonstrate the benefit of stereotactic radiotherapy on outcomes like visual acuity.

The CCG is aware that larger, longer term trials are in progress, including one in the UK, the STAR trial (NCT02243878).

Until more robust evidence for clinical, safety and cost-effectiveness is available, Telford and Wrekin CCG considers the use of stereotactic radiotherapy in wet age-related macular degeneration to be a LOW PRIORITY intervention that is not routinely commissioned.

This position will be reviewed when new clinical evidence or national guidance (e.g. NICE) is published.

Additional information
The current (published in 2014) guideline on AMD from European specialist comment on the technique but states: 'At present, the only scientific argument to support the use of irradiation for the treatment of neovascular AMD is the reduction in the number of retreatments necessary, but its delivery methods, efficacy and safety results are still controversial and need further investigation'
http://bjo.bmj.com/content/98/9/1144.full.pdf+html

1 Jackson T.L et al. Stereotactic Radiotherapy for Neovascular Age-Related Macular Degeneration – 52 week safety and efficacy results of the INTREPID Study. OphthalmoGray 2013; 120: 1893-1900
3 Jackson T.L. et al. Stereotactic Radiotherapy for Neovascular Age-Related Macular Degeneration – Year 2 Results of the INTREPID Study. OphthalmoGray 2014; 1-8