NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview radiotherapy for age-related macular degeneration

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee advise on the safety and efficacy of an interventional procedure previously reviewed by SERNIP. It is based on a rapid survey of published literature, review of the procedure by specialist advisors and review of the contents of the SERNIP file. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in December 2002.

Procedure names

- Radiotherapy for neovascular age-related macular degeneration.

Specialty societies

Royal College of Opthalmology

Description

Indications

Age-related macular degeneration is the commonest cause of irreversible blindness in developed countries. The prevalence of macular degeneration rises with age, from about 0.7% in people aged 40 to 50 years, to 27% in people over the age of 90 years.[1] In 1996 there were 738,850 people over 65 registered blind or partially sighted in England. About 80%, or about 600,000, are likely to have age-related macular degeneration (Source: Royal National Institute for the Blind). The cause is unknown.

The macula is the part of the retina that provides central vision. Ninety per cent of people with age related macular degeneration have atrophic, or 'dry', macular degeneration, characterised by thinning of the macular retina. The other 10% have neovascular macular degeneration (also known as 'wet' or exudative macular degeneration). This type is characterised by the growth of new vessels in the choroid layer underneath the retina, which can threaten vision if they leak and cause scarring. The new vessels are described according to whether they can be seen clearly ('classic') or poorly ('occult') on a test called fluoroscein angiography. Occult new vessels probably lie more deeply in the choroid than classic new vessels. New vessels in the foveal part of the choroid (subfoveal vessels) are potentially the most disabling, because the fovea is the central part of the macula, which is responsible for the sharpest vision.

The visual prognosis of wet macular degeneration is poor. Without treatment, 40% of people with occult neovascularisation develop severe visual loss within 2 years

(www.rcophth.ac.uk). People with neovascularisation in one eye have about a 50% chance of developing a similar lesion in the fellow eye within 5 years.

Changes in visual acuity are usually measured by changes in the number of lines seen on a Snellen chart.

Summary of procedure

Lasers have been used for several years to coagulate new vessels in 'wet' macular degeneration. However, the procedure itself may permanently impair vision, especially if the vessels are very close to the fovea (subfoveal). Recurrence is common. Laser therapy appears only to work in people with classic neovascular macular degeneration (macular degeneration associated with 'classic' type new vessels). Radiotherapy may destroy new vessels as effectively as laser treatment, but with less risk of permanent visual loss, and may also work in people with occult new vessels.

Radiotherapy is usually given as a day treatment. The beam of radiotherapy is angled to avoid damage to the optic nerve and structures in the other eye. The radiation dose is measured in Grays (Gy).

Potential risks of radiotherapy include: cataract (clouding of the lens); phosphenes (flashing lights or spots); dry eyes; damage to the optic nerve; and damage to the retina.

Other new treatments for macular degeneration include surgery to remove the new vessels, macular translocation, photodynamic therapy; and new drugs that suppress new vessel formation (antiangiogenic drugs).

Literature review

Appraisal criteria

We included studies on radiotherapy in people with wet (neovascular) age-related macular degeneration.

List of studies found

Nine randomised controlled trials were found. The table gives details of the five largest.[2-6]

Eleven other studies that included at least 100 people were found: three non-randomised controlled studies and eight case series.

Appendix A gives references to the four smaller randomised controlled trials and the 11 other studies.

Table 1 Summary of key efficacy and safety findings (1)

Study details	Key efficacy findings	Key safety findings	Key reliability and validity issues

Study details	Key efficacy findings	Key safety findings	Key reliability and validity issues
Holz FG[2] Randomised controlled trial Multicentre study in Germany 1996 to 1997 n = 205 people with subfoveal new vessels: n = 101: 8 treatments with 2 Gy radiotherapy, average age 72 n = 104: 8 treatments 0 Gy (sham) , average age 75 Inclusion criteria: • aged 50 or older • new vessels < 6 times size optic disc Exclusion criteria: • other eye disease • retinal haemorrhage • previous: laser coagulation; photodynamic therapy; antiangiogenic drugs Follow up: 12 months	Mean reduction in visual acuity: radiotherapy: 3.5 lines sham: 3.7 lines p = 0.53 Loss of 3 or more lines of visual acuity: radiotherapy: 51% sham: 53% p = 0.88	Phosphenes during treatment (number of people): radiotherapy: 2 sham: 1 Cataract (number of people): radiotherapy: 7 sham: 7 p = 0.22 Dry eye symptoms (number of people): radiotherapy: 30 sham: 38 p = 0.56	Randomisation appropriate. Included people with classic and occult new vessels. Power reasonable for efficacy outcomes, but not for safety outcomes. Radiotherapy group slightly older and more likely to be male. Blinding of study participants and those measuring outcomes. Outcomes generally appropriate, although clinical relevance not clear. Follow up of reasonable length. Losses to follow up: radiotherapy: 12 sham: 7

Study details	Key efficacy findings	Key safety findings	Key reliability and validity issues
Hart PM[3] Randomised controlled trial Multicentre study UK 1995 to 1998 n = 203 people with subfoveal new vessels n = 99: 12Gy radiotherapy, mean age 75 n = 100: observation, mean age 75 Inclusion criteria: • aged 60 or older • visual acuity 20/200 or better • Exclusion criteria: • haemorrhage • other eye disease • diabetes mellitus, hypertension • previous radiotherapy to either eye Follow up: 24 months	Loss of 3 or more lines of distance visual acuity: radiotherapy: 70% observation: 82% p = 0.08 Loss of 3 or more lines of near visual acuity: radiotherapy: 67% observation: 72% p = 0.47	Radiation retinopathy: none Tests of tear production showed reduction in radiotherapy group compared with observation group; clinical outcomes not described	Randomisation not described. Most people had classic new vessels.. No major differences between groups. Power reasonable for efficacy outcomes, but not for safety outcomes. Study participants not blind to allocation; those measuring outcomes blind to allocation. Outcomes generally appropriate, though clinical relevance not clear. Follow up of reasonable length. Losses to follow up:. radiotherapy: 14 observation: 14

Study details	Key efficacy findings	Key safety findings	Key reliability and validity issues
Valmaggia C[4] Randomised controlled trial St Gallen, Switzerland 1994 to 1999 n = 161 people with subfoveal new vessels n = 57: 8Gy radiotherapy, average age 76 n = 52: 16Gy radiotherapy, average age 76 n = 52: 1Gy radiotherapy, average age 75 (controls) Inclusion criteria: • rapid worsening of visual acuity Exclusion criteria: • other eye diseases • haemorrhage • serous pigment epithelial detachment Follow up: 18 months	Mean number of lines lost visual acuity: 16 Gy: 1.9 (versus control: p = 0.05) 8 Gy: 1.7 (versus control: p = 0.01) control: 3.2 Mean number of lines lost in reading ability: 16 Gy: 2.4 (versus control: p = 0.38) 8 Gy: 1.4 (versus control: p = 0.14) control: 2.7	Ocular irritation: none Conjunctivitis: none Dry eyes: none Cataract: none Radiation retinopathy: none Optic nerve damage: none	Randomisation not fully described. Included people with classic and occult new vessels. Power calculation reasonable for efficacy outcomes. No major differences between groups in baseline characteristics. Study participants and those measuring outcomes blind to allocation. Outcomes generally appropriate, although clinical relevance not clear. Follow up of reasonable length. Losses to follow up: 16 Gy: 9 8 Gy: 6 control: 9

Study details	Key efficacy findings	Key safety findings	Key reliability and validity issues
Kobayashi H[5] Randomised controlled trial Hyogo, Japan Date not stated (published 2000) n = 101 people with subfoveal new vessels n = 51:10 treatments 20 Gy radiotherapy, average age 71 n = 50: observation only, average age 71 Inclusion criteria: • newly formed new vessels • visual acuity 25/50 or worse • age 60 or older Exclusion criteria: • other eye diseases • other systemic disorders Follow up: 2 years	Change in mean visual acuity: radiotherapy: 20/99 to 20/168 control: 20/89 to 20/328 Test of significance not reported Change in visual acuity (measured by logarithm of minimum angle of resolution): radiotherapy: 0.23 control: 0.56 $p < 0.0001$	Control group complications: none Radiotherapy (number people): • conjunctival infection: 2 • cataract: 1 • optic nerve damage: 0 • radiation retinopathy: 0	Computer-generated randomisation. Power reasonable for efficacy outcomes. Included people with classic and occult new vessels. Fewer people with classic new vessels in control group. Assessor of outcome blind to allocation. Outcomes generally appropriate, though clinical relevance not clear.. Follow up of reasonable length. Losses to follow up: radiotherapy: 6 control: 10.

Study details	Key efficacy findings	Key safety findings	Key reliability and validity issues
Marcus DM[6] Randomised controlled trial Georgia, USA 1995 to 1998 n = 83 eyes with subfoveal new vessels n = 42: 14 Gy radiotherapy in 7 sessions, average age 75 n = 41: 1 session of sham radiotherapy, average age 77 Inclusion criteria: • new vessels under centre of foveal avascular zone • visual acuity no worse than 20/400 • aged 48 or older Exclusion criteria: • diabetes • other retinal vascular disease • other systemic disorders • previous laser therapy or radiotherapy Follow up: 1 year	Change in median distance visual acuity: radiotherapy: 20/80 to 20/320 control: 20/125 to 20/250 p = 0.59 Mean lines lost of visual acuity: radiotherapy: 4.1 control: 3.4 p = 0.35	Radiation retinopathy: 0 Optic neuropathy: 0 Phosphenes: 0 *[* Retinal detachment radiotherapy: 1 control: 0 Vitreous haemorrhage: radiotherapy: 1 control: 0 Cataract: radiotherapy: 28 control: 12 p = 0.99	Block randomisation method described. Power limited. Included people with classic and occult new vessels. Baseline characteristics between groups compared. Study participants and those measuring outcomes blind to allocation. Outcomes generally appropriate, though clinical relevance not clear. Follow up of reasonable length. Losses to follow up: radiotherapy: 9 control: 4

Validity and generalisability of the studies

- The studies described in the table were all carried out in settings applicable to the UK. All were randomised controlled trials of good quality. The outcomes in all studies were appropriate, though none provide any measure of the study participants' self-rated assessment of their vision.
- Three studies found no evidence that radiotherapy reduced deterioration in visual acuity more than sham treatment or observation only,[2,3,6] although the third study may have lacked power to demonstrate statistically significant effects.[6]
- Two studies found that radiotherapy reduced loss of visual acuity compared with very low dose (effectively sham) radiotherapy[4] or observation only.[5] Both included people with classic and occult new vessels. The effect size appeared to be small and the relevance of these effects to functional ability or quality of life is not clear.

Bazian comments

- None.

Specialist advisors' opinions

Specialist advice was sought from the *Royal College of Opthalmology*

- Trials have shown little or no benefit of radiotherapy.
- Any patients being treated are enrolled in clinical trials.
- Any effect likely to be modest.

Issues for consideration by IPAC

- None other than those discussed above.

References

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Holz FG, Engenhart-Cabillic R, Unnebrink K, Bellmann C, et al. A prospective, randomized, double-masked trial on radiation therapy for neovascular age-related macular degeneration (RAD study). Ophthalmology 1999; 106: 2239–47

Hart PM, Chakravarthy U, Mackenzie G, Chisholm IH, et al. Visual outcomes in the subfoveal radiotherapy study: a randomized controlled trial of teletherapy for age-related macular degeneration. Archives of Ophthalmology 2002; 120: 1029–38

Valmaggia C, Ries G, Ballinari P. Radiotherapy for subfoveal choroidal neovascularization in age-related macular degeneration: a randomized clinical trial. American Journal of Ophthalmology 2002; 133: 521–9

Kobayashi H, Kobayashi K. Age-related macular degeneration: Long-term results of radiotherapy for subfoveal neovascular membranes. American Journal of Ophthalmology 2000; 130: 617–35

Marcus DM, Sheils W, Johnson MH, McIntosh SB, et al. External beam irradiation of subfoveal choroidal neovascularization complicating age-related macular degeneration: one-year results of a prospective, double-masked, randomized clinical trial. Archives of Ophthalmology 2001; 119: 171–80

Appendix A: References to studies not described in the table

Reference	Number of study participants
Randomised controlled trials	
Anders N, Stahl H, Dorn A, Walkow T, et al. Radiotherapy of exudative senile macular degeneration. A prospective controlled study. [German]. *Ophthalmologe* 1998; 95: 760–4	76
Bergink GJ, Hoyng CB, van der Maazen RW, Vingerling JR, et al. A randomized controlled clinical trial on the efficacy of radiation therapy in the control of subfoveal choroidal neovascularization in age-related macular degeneration: radiation versus observation. *Graefes Archive for Clinical & Experimental Ophthalmology* 1998; 236: 321–5	74
Kacperek A, Briggs M, Sheen MA, Damato BE, et al. Macular degeneration treatment at Clatterbridge centre for oncology: Treatment and preliminary results. *Physica Medica* 2001; 17 (Suppl 3): 7–9	58
Char DH, Irvine AI, Posner MD, Quivey J, et al. Randomized trial of radiation for age-related macular degeneration. *American Journal of Ophthalmology* 1999; 127:574–8	27
Non-randomised studies	
Spaide RF, Guyer DR, McCormick B, Yannuzzi LA, et al. External beam radiation therapy for choroidal neovascularization. *Ophthalmology* 1998; 105: 24–30	210
Postgens H, Bodanowitz S, Kroll P. Low-dose radiation therapy for age-related macular degeneration. *Graefes Archive for Clinical & Experimental Ophthalmology* 1997; 235: 656–61	174
Subasi M, Akmansu M, Or M. Treatment of age-related subfoveal neovascular membranes by teletherapy: results of a non-randomized study. *Radiation Medicine* 1999; 17: 169–73.	103
Case series	
Chakravarthy U, Mackenzie G. External beam radiotherapy in exudative age-related macular degeneration: A pooled analysis of phase I data. *British Journal of Radiology* 2000; 73: 305–13	409
Staar S, Krott R, Mueller RP, Bartz-Schmidt KU, Heimann K. External beam radiotherapy for subretinal neovascularization in age-related macular degeneration: is this treatment efficient? *International Journal of Radiation Oncology, Biology, Physics* 1999; 45: 467–73	287
Brady LW, Freire JE, Longton WA, Miyamoto CT, et al. Radiation therapy for macular degeneration: technical considerations and preliminary results. *International Journal of Radiation Oncology, Biology, Physics* 1997; 39: 945–8.	278
Mauget-Faysse M, Coquard R, Francais-Maury C, Milea D, et al. Radiotherapy for age-related macular degeneration: risk factors of complications, prevention and treatment of side-effects. [French]. *Journal Francais d'Ophtalmologie* 2000; 23:127–36	270
Mauget-Faysse M, Chiquet C, Milea D, Romestaing P, et al. Long term results of radiotherapy for subfoveal choroidal neovascularisation in age related macular degeneration. *British Journal of Ophthalmology* 1999; 83: 923–8.	212
Spaide RF, Leys A, Herrmann-Delemazure B, Stalmans P, Tittl M, Yannuzzi LA et al. Radiation-associated choroidal neovasculopathy. *Ophthalmology* 1999; 106: 2254–60	193
Schittkowski M, Schneider H, Gruschow K, Ziegler PG,. 3 years experience with low dosage fractionated percutaneous teletherapy in subfoveal neovascularization. Clinical results. [German]. *Strahlentherapie und Onkologie* 2001; 177: 345–53	118
Stalmans P, Leys A, Van Limbergen E. External beam radiotherapy (20 Gy, 2 Gy fractions) fails to control the growth of choroidal neovascularization in age-related	111

macular degeneration: a review of 111 cases. *Retina* 1997; 17: 481–92	

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