Radiotherapy for neovascular age-related macular degeneration (Review)

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[Intervention Review]

Radiotherapy for neovascular age-related macular degeneration

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ABSTRACT

Background

Radiotherapy has been proposed as a treatment to prevent new vessel growth in people with neovascular age-related macular degeneration (AMD).

Objectives

The aim of this review was to examine the effects of radiotherapy on neovascular AMD.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group trials register) on *The Cochrane Library* Issue 2, 2004, MEDLINE (1966 to May 2004), EMBASE (1980 to June 2004) and LILACS (Latin American and Caribbean Health Sciences Literature Database) (May 2004). We also wrote to investigators of trials included in the review to ask if they were aware of any other studies.

Selection criteria

We included all randomised controlled trials in which radiotherapy was compared to another treatment, sham treatment, low dosage irradiation or no treatment in people with subfoveal choroidal neovascularisation secondary to AMD.

Data collection and analysis

Two reviewers independently extracted the data. Relative risks were combined using a random effects model. The percentage of the variability in effect estimates that was due to heterogeneity, rather than sampling error, was estimated using I^2.

Main results

Eleven trials randomising a total of 1078 people were included in this review. All trials used a similar method of delivering the radiotherapy treatment (external beam). Dosage ranged from 7.5 to 24 Gy. Most trials found effects (not always significant) that favoured treatment. However, there was considerable inconsistency in the results between trials (I^2 > 50%). As only 11 trials were included in the review and only some of these trials provided data for each outcome our ability to determine the causes of the heterogeneity between trials was limited. Subgroup analyses did not reveal any statistically significant interactions although with small numbers of trials in each subgroup (range two to four) this was not surprising. There was some indication that trials with no sham irradiation reported a greater effect of treatment as did trials with a greater percentage of participants with classic choroidal neovascularisation.

Authors' conclusions

This review currently does not provide evidence that external beam radiotherapy is an effective treatment for neovascular AMD. If further trials are to be considered to evaluate radiotherapy in AMD then adequate masking of the control group must be considered. Given the recent evidence that most lesions are amenable to treatment with photodynamic therapy if identified at a small lesion size, trials evaluating radiotherapy against photodynamic therapy are warranted.

PLAIN LANGUAGE SUMMARY

Radiotherapy for neovascular age-related macular degeneration

The macula is the central area of the retina used for detailed vision. Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world, particularly in the elderly, and can be associated with new blood vessel growth under the retina of the eye, termed subfoveal choroidal neovascularisation (CNV). The present treatment of choice is photodynamic therapy (PDT) with verteporfin. Radiotherapy has been proposed to prevent new vessel growth. This review found that most trials showed effects (not always significant) that favoured treatment with radiotherapy but with inconsistencies in the results. Radiotherapy has potential risks of systemic morbidity and exposure to the fellow eye.

BACKGROUND

Introduction

The macula, the central area of the retina, is used for detailed vision such as reading, recognising faces and driving. Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world. It is difficult to get a clear definition of AMD. The term 'age-related' is used partly due to its unknown pathogenesis. It is believed that both genetic and environmental factors play a significant role in the development of the disease. From a clinical perspective, AMD primarily affects the macular region. The term 'degeneration' is used to distinguish AMD from other genetic macular dystrophies which run in families and those where there is a clear environmental cause such as an infection or trauma.

There are several signs appearing in the retina that are associated with increasing age and increased risk of developing age-related macular degeneration. These signs, known as age-related maculopathy (ARM), include the presence of drusen (yellow spots beneath the retina), pigmentary disturbance and small focal areas of atrophy. In general, ARM is not associated with significant visual loss. Some people with ARM will go on to develop AMD.

Epidemiology

The prevalence of ARM is about 30% in the over 70 age group. The reported prevalence of AMD varies significantly between several large scale epidemiological studies, partly due to the inconsistency in terminology used. It is, however, clearly increasing with age. Although it was reported that females are more likely to suffer from AMD, after correction for age and life expectancy the gender difference is not significant (Evans 2001). In the UK, approximately 30,000 people are registered blind or partially sighted every year, half of whom will have macular degeneration (Evans 1995).

Presentation

Classification of AMD has been controversial. Currently accepted definitions distinguish those people who have geographic atrophy (large area of atrophy centred in the macula) and those with choroidal neovascularisation (CNV). This review is concerned with treatment for neovascular AMD.

In neovascular (wet) AMD, CNV develops beneath the retina. In the initial phase the CNV might cause visual distortion due to leakage of fluid into the surrounding retina. At this stage the retinal function is only mildly affected and the CNV is potentially reversible. However, the CNV may leak serum lipid and protein leading to exudation and significant swelling of the retina. The CNV may bleed and the haemorrhages may be toxic. Both exudation and haemorrhages induce a scarring response. These are associated with extensive damage to the architecture of the retina-retinal pigment epithelium-choroid complex, leading to significant visual loss.

Choroidal neovascularisation is defined as classic or occult according to its appearance on fluorescein angiography, where fluorescent dye is injected intravenously and imaged as it passes through

the blood vessels of the eye. Classic membranes are clearly delineated and can be seen at the early frames of the angiogram. Occult membranes present as either late leakage, which cannot be seen in the early frames, or fibrovascular pigment epithelial detachment. Most lesions have both classic and occult components.

Treatment options

The Macular Photocoagulation Study Group (MPSG 1994) has shown that laser photocoagulation of classic extrafoveal and juxtafoveal CNV (those not directly underneath the fovea at the centre of the macula) could delay the loss of vision. However, most patients present with subfoveal CNV (those where a component of the CNV extends underneath the fovea) and whilst photocoagulation can limit the extent of the subsequent visual loss it causes immediate loss of central vision due to the concurrent destruction of the overlying retina. Laser therapy for subfoveal CNV is rarely performed in practice.

Photodynamic therapy (PDT) has been investigated to treat CNV without affecting the retina. Photoreactive chemicals are injected into the patient and irradiated with light as they pass through the CNV. This light is strong enough to activate the chemicals, causing them to emit free radicals that destroy the blood vessels, but is not strong enough to cause damage to the overlying retina. The TAP Study Group (Bressler 2001; TAP Study 1999) has shown that PDT is effective for patients with 100% classic CNV. The effectiveness for predominantly classic, but not 100% classic CNV, is more debatable. It is not effective for predominantly occult CNV. A systematic review of PDT for AMD is published on *The Cochrane Library* (Wormald 2004).

Radiotherapy is commonly used in oncology. The use of radiotherapy in non-neoplastic diseases is increasingly common. It is believed that it can preferentially damage dividing and fast growing cells more than normal supporting cells. In rats, photoreceptor cell death is not seen at doses less than 10 Gy and the retinal pigment epithelial cell loss does not occur under 20 Gy in single-fraction. There is also evidence to suggest that fractionation of irradiation greatly reduces the toxicity but preserves the DNA-damaging effects in rapidly dividing cells. Clinical experience suggested that cumulative doses of up to 25 Gy cause no damage to the retina or optic nerve. As the endothelial cells in CNV are dividing it is possible that radiotherapy can stop the growth of CNV without significant damage to the retina.

Rationale for a systematic review

There are several randomised controlled trials of radiotherapy for neovascular AMD using different dosage and fractionation schemes. The aim of this review was to systematically assess the results of these studies with a view to providing an overall estimate of treatment effect.

OBJECTIVES

The aim of this review was to examine the effects of radiotherapy on neovascular AMD.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

We included trials in which participants were people with choroidal neovascularisation (CNV) secondary to AMD as defined by the study investigators.

Types of interventions

We included studies in which radiotherapy, no matter how it was delivered, was compared to another treatment, low dosage irradiation, sham treatment or no treatment.

Types of outcome measures

Primary outcomes

The primary outcome for this review was loss of visual acuity. We considered two measures of loss of visual acuity - three or more lines lost on a logMAR chart (equivalent to doubling of visual angle) and six or more lines lost (equivalent to quadrupling of visual angle). We also considered mean visual acuity and change in visual acuity as a continuous score.

Secondary outcomes

The secondary outcomes for this review were:

- measures of contrast sensitivity;
- new vessel growth;
- quality of life measures - any validated measurement scale which aims to measure the impact of visual function loss on quality of life of participants;
- any adverse outcomes as reported in trials.

Follow up

We measured outcomes at 6, 12 and 24 months after radiation treatment.

Search methods for identification of studies

Electronic searches

Trials were identified from the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group trials register) on *The Cochrane Library*, MEDLINE, EMBASE and LILACS (Latin American and Caribbean Health Sciences Literature Database). There were no language restrictions in the searches.

See: Appendices for details of search strategies for each database.

Searching other resources

We contacted the investigators of the trials included in this review for information about further trials. We searched the reference lists of relevant studies for further trial reports. We did not perform manual searches of conference proceedings or journals.

Data collection and analysis

Finding the trials

Two reviewers independently scanned the titles and abstracts resulting from the searches. We obtained full copies of all potentially or definitely relevant articles. Two reviewers assessed the full copies according to the 'Criteria for considering studies for this review'. Only articles meeting these criteria were assessed for quality.

Assessment of methodological quality

Two reviewers independently assessed study quality according to methods set out in Section 6 of the Cochrane Reviewers' Handbook. The reviewers were not masked to any trial details during the assessment. Four parameters of quality were considered when grading the articles: allocation concealment and method of allocation to treatment; masking of providers and recipients of care; masking of outcome assessment; and completeness of follow up. We graded each parameter of trial quality: A - adequate; B - unclear; or C - inadequate. We resolved disagreement between the reviewers on assessments by discussion. We contacted the trial authors for clarification on any parameter graded B - unclear. We excluded any trial scoring C - inadequate on allocation concealment and method of allocation to treatment.

Data collection

Two reviewers independently extracted data using a form developed by the Cochrane Eyes and Vision Group. Discrepancies were resolved by discussion. One reviewer entered data into RevMan 4.2 using the double data-entry facility to check for errors.

Data synthesis

The primary outcome of visual acuity loss was assessed at 6, 12 and 24 months. We used two outcomes, loss of three or more lines on a logMAR chart (equivalent to a doubling of the visual angle) and loss of six or more lines (quadrupling of the visual angle). As the proportion of people experiencing this outcome was high in the control group (more than 10%) we used the relative risk as our effect measure. Not all trials reported visual acuity outcomes in this dichotomous format. We contacted investigators for data but these requests were not successful. We, therefore, also included mean visual acuity and change in visual acuity as a continuous score.

There was considerable statistical heterogeneity between studies. However, the amount of heterogeneity varied with the outcome. We have included the pooled analyses and I^2 estimates on the graphs for information but have not reported the pooled results in the abstract. We used a random effects model to combine results. Not all of the trials reported data for all outcomes. This meant that our options for exploring the sources of heterogeneity were limited. In our protocol we specified three factors as of interest for subgroup analyses (method of delivery, dosage and type of CNV). All trials used the same method of delivery.Table 1 shows the details of dosage in the trials and Table 2 shows the details of CNV. During the course of doing the review we identified one additional aspect of study design as of interest for subgroup analysis. This was whether or not sham irradiation was carried out in the control group.

Using these factors we performed stratified analyses, the purpose of which was to determine whether the outcome varied significantly with type of explanatory variable. We used data from the 12 month follow-up and divided the trials into two groups for each factor: high dose (more than 14 Gy) versus low dose (less than or equal to 14 Gy); 50% or more of participants with classic CNV versus less than 50% with classic CNV; and trials with no sham irradiation versus those with sham irradiation. As the numbers of trials were small and the purpose of this analysis was to compare treatment effects only, we used odds ratios pooled using a fixed effect model. We calculated an 'interaction effect' (Altman 2003) i.e. compared the pooled odds ratio in the two subgroups.

There were not enough data reported for other potential outcome measures (growth of new vessels, contrast sensitivity and quality of life) to enable a statistical analysis but these are discussed in the results section.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Finding the trials

The searches identified 149 reports. A further two potentially relevant reports were identified by subsequent electronic searching carried out for another project. We obtained full copies of 28

reports which referred to 23 potentially relevant studies. We excluded 12 of these trials largely because the treatment groups were not randomly allocated (*see* 'Characteristics of excluded studies' table). A total of 11 trials were considered suitable for inclusion in the review (*see* 'Characteristics of included studies' table). For the excluded studies the authors did not use the word "randomised" ie they had two groups but one, for example, was retrospectively identified.The included studies all stated that they were randomised controlled trials but did not always specify how they performed the randomisation (see below).

Types of participants

The 11 trials randomised a total of 1078 people. The studies took place in Germany (Anders 1998; Eter 2002; RAD 1999), the Netherlands (Bergink 1998), USA (Char 1999; Ciulla 2002; Marcus 2001), Japan (Kobayashi 2000), UK (Kacperek 2001; SFRADS 2002) and Switzerland (Valmaggia 2002). In all studies the mean age of participants was approximately 75 years and in most studies the majority of participants were women (range from 38% to 64%).

All studies recruited participants with subfoveal CNV associated with AMD. Most studies, with the exception of Anders 1998 and Kacperek 2001, classified the CNV lesion as classic, occult or mixed. In most trials the percentage of participants with classic or predominantly classic CNV ranged between 37% and 57% (Table 2); in Marcus 2001 a lower percentage of participants with classic CNV was recruited (12%).

Two studies did not specify visual acuity criteria for entry to the trial (Eter 2002; Valmaggia 2002). Most studies specified that eligible participants should have a worst visual acuity in the study eye, usually between 6/60 and 6/120 (Anders 1998; Bergink 1998; Ciulla 2002; Kacperek 2001; Marcus 2001; RAD 1999; SFRADS 2002); two studies did not specify a worst acuity (Char 1999; Kobayashi 2000). Four studies specified that there should be some visual loss, usually to 6/12 or less (Anders 1998; Char 1999; Ciulla 2002; Kobayashi 2000).

Types of intervention

Table 1 shows the dosage of radiotherapy applied in the different studies. The dosage ranged from 24 Gy (four fractions of 6 Gy) (Bergink 1998) to 7.5 Gy (one fraction) (Char 1999). Seven of the studies gave no treatment to the control group (Anders 1998; Bergink 1998; Char 1999; Eter 2002; Kacperek 2001; Kobayashi 2000; SFRADS 2002); three studies used sham irradiation (Ciulla 2002; Marcus 2001; RAD 1999) and one study used very low-dose irradiation (1 Gy) (Valmaggia 2002).

Types of outcome measures

In all studies the primary outcome was visual acuity. In most cases this was measured using the ETDRS chart or equivalent logMAR chart. The exception to this was Bergink 1998 where Snellen acuity was measured. Most studies considered some aspect of the clinical progression of CNV such as area of CNV (Kobayashi 2000; Valmaggia 2002) and appearance of the fundus on fluorescein angiography (Marcus 2001; RAD 1999). Near vision (SFRADS 2002) and reading ability (Valmaggia 2002) were also considered. Two studies specifically considered safety (Kobayashi 2000; SFRADS 2002).

Risk of bias in included studies

Table 3 shows the results of assessment of study quality.

In four studies (Kobayashi 2000; Marcus 2001; RAD 1999; SFRADS 2002) trial reports indicated that randomisation had been executed properly, that is, an unpredictable sequence of treatment allocation was concealed properly from people recruiting participants into the trial.

Studies that did not perform sham irradiation (Anders 1998; Bergink 1998; Char 1999; Eter 2002; Kacperek 2001; Kobayashi 2000; SFRADS 2002) were at greater risk of performance bias with participants and providers in general being aware of the treatment group. However, in three of these studies efforts were made to mask the outcome assessor to treatment group (detection bias) (Char 1999; Kobayashi 2000; SFRADS 2002).

Follow-up rates were not described clearly in three studies (Bergink 1998; Char 1999; Kacperek 2001) and were slightly lower in the control group in a further two studies (Kobayashi 2000; Marcus 2001). In one study (SFRADS 2002) a strictly intention-to-treat analysis was not performed as one patient randomised to the control group received treatment and was analysed in the treatment group. However, this was unlikely to have had a major impact on the results of the study. None of the authors included people lost to follow up in the analyses.

Effects of interventions

Primary outcomes

Data on visual acuity were not available in a form suitable for inclusion in the review for two studies (Eter 2002; Kacperek 2001). In Eter 2002 45 eyes of 45 patients were assigned in a ratio of 2:1 to either radiation treatment (20 Gy in 10 fractions) or observation. There were no statistically significant differences between treatment and control groups six months after treatment. In Kacperek 2001 38 people were treated with radiotherapy (18 Gy in 4 fractions) and compared to 28 people who were not treated. At 12 months visual acuity was measured on 28 participants in the treatment group and 20 in the control group. Participants in the control group had lost more vision than the treatment group (Mann Whitney test p = 0.028).

Follow up at six months

Three trials provided data on the primary outcome (three or more lines visual acuity lost) at six months (Marcus 2001; SFRADS 2002; Valmaggia 2002). There was considerable inconsistency in trial results. The I^2 value (percentage of total variation across stud-

ies that was due to heterogeneity rather than chance) (Higgins 2003) was 59.2%. The relative risk of losing three or more lines six months after treatment varied from 0.40 (95% CI 0.18 to 0.88) (Valmaggia 2002) to 1.06 (95% CI 0.71 to 1.57)(Marcus 2001). There was less, but still substantial, heterogeneity in the outcome six or more lines visual acuity lost (I^2 = 42.6%) with the relative risk varying from 0.07 (95% CI 0.0 to 1.11) (Valmaggia 2002) to 0.83 (95% CI 0.47 to 1.46) (SFRADS 2002).

Follow up at 12 months

Six trials provided data on visual acuity outcomes at 12 months (Bergink 1998; Char 1999; Marcus 2001; RAD 1999; SFRADS 2002; Valmaggia 2002). Again there was considerable inconsistency in trial results for the outcome of three or more lines visual acuity lost (I^2 = 59.0%) with the relative risk varying from 0.37 (95% CI 0.15 to 0.90) (Char 1999) to 1.22 (95% CI 0.91 to 1.62) (Marcus 2001). There was less inconsistency for the outcome of six or more lines visual acuity lost (I^2 = 43.3%) with the relative risk ranging from 0.21 (95% CI 0.07 to 0.68) (Bergink 1998) to 1.23 (95% CI 0.56 to 2.68) (Marcus 2001).

Follow up at 24 months

Three trials provided data on visual acuity outcomes at 24 months (Kobayashi 2000; SFRADS 2002; Valmaggia 2002). There was considerable inconsistency in trial results for the outcome of three or more lines lost (I^2 = 58.3%). However, in contrast to previous follow up times and outcomes there was no inconsistency in trial results for the outcome of six or more lines lost (I^2 = 0%). The pooled relative risk was 0.76 (95% CI 0.58 to 1.01). This result approached statistical significance. Using a fixed effect model the relative risk was 0.75 (95% CI 0.56 to 0.99) which was marginally statistically significant (p = 0.04).

Visual acuity as a continuous outcome

Not all trials reported visual acuity outcomes in a dichotomous format. In order to include data from the trials that did not, we also collected data on logMAR visual acuity as a continuous variable. These data were available for most trials at 12 months, either as mean visual acuity at follow up or change in visual acuity since the start of the trial. There was less heterogeneity in these outcomes. For example, for the trials reporting change in visual acuity, the I^2 value was 12.2%. The pooled weighted mean difference was 0.02 (95% CI -0.06 to 0.11). These results were consistent with a mean change in visual acuity of -0.06 (less than one line of visual acuity in favour of the treated group) to 0.11 (approximately one line of visual acuity in favour of the control group).

Sensitivity analysis

With only 11 trials included in the review and only some of these trials providing data for some outcomes our ability to determine the causes of the heterogeneity or inconsistency between trials was limited. Using the factors prespecified in the protocol (dosage and type of CNV) and one factor not prespecified in the protocol (sham irradiation in the control group) we performed stratified analyses for the visual acuity outcome (three or more lines lost) at 12 months (because this was the time period for which most data were available) (*see* Table 4). There were no statistically significant interactions. There was some indication that trials with no sham irradiation reported a greater effect of treatment as did trials with a greater percentage of participants with classic CNV. There was little evidence for any effect of dosage.

Secondary outcomes

Our secondary outcome measures included change in membrane size and contrast sensitivity. Of the trials that specifically studied change in lesion size a beneficial outcome for treatment was found by one (Kobayashi 2000). No difference in the growth rate between treatment and controls were reported by four trials (Bergink 1998; Char 1999; Marcus 2001; Valmaggia 2002). Of the trials that specifically studied changes in contrast sensitivity, SFRADS 2002 reported a statistically significant difference in the loss of 0.3 log units of contrast sensitivity in favour of treatment at 24 months but not 3 months. No statistically significant difference in contrast sensitivity between treated and control groups were reported by Marcus 2001.

Adverse effects

The incidence of adverse events was low in all the trials reviewed. Three trials found slightly higher rates of cataract progression in the treatment groups but this was not statistically significant (Kobayashi 2000; Marcus 2001; RAD 1999).

There were no reported cases of radiation retinopathy, optic neuropathy or the development of malignancy. However, the duration of follow up was likely to be too short to detect this. Given the mean age of participants this may not be a major concern.

Although there was an overall beneficial effect for treatment with regard to vision Bergink 1998 reported a drop in central vision with a loss of three or more lines in a substantial proportion of patients in the treatment group. This was not reported by trials using standard fractions (2 Gy) in the treatment protocol.

Other complications reported in the treatment group included one case of rhegmatogenous retinal detachment and one case of a large non-clearing vitreous haemorrhage (Marcus 2001); transient conjunctival injection in two participants (Kobayashi 2000); and transient disturbance of the precorneal tear film, found to be significant (SFRADS 2002).

DISCUSSION

We identified 11 trials of the effect of radiotherapy on neovascular AMD, which randomised 1078 participants. Not all of these trials could be included in each of our planned analyses because of differences in the way outcomes were presented and follow-up times.

There was considerable clinical and statistical inconsistency between trials. This heterogeneity meant that we were unable to present a pooled estimate of treatment effect. Most trials found effects that favoured treatment, but these were not always signif-

icant. The exception was Marcus 2001 which consistently found non-significant effects that favoured the control group. It is difficult to ascertain why this trial should be different but it had sham irradiation in the control group and a very low percentage of participants with classic CNV (12%).

With only 11 trials in the review and differences between trials in terms of outcome reporting it was difficult to explore the sources of heterogeneity. Subgroup analyses comparing groups of trials with different attributes (i.e. low versus high dosage; low versus high percentage with classic CNV; and sham irradiation versus observation of the control group) did not reveal any statistically significant interactions. With small numbers of trials in each subgroup (range two to four) this was not surprising.

It is encouraging that there were no significant adverse effects noted with up to 20 Gy of radiotherapy deployed in 2 Gy fractions. The occurrence of severe visual loss in some treated patients receiving 24 Gy in larger fractions questions the safety of higher doses. Higher doses of radiation are associated with greater morbidity such as radiation retinopathy and optic neuropathy. Given the lack of a clear benefit of higher doses it cannot be assumed that these may be used safely in clinical practice. The long-term risk to the fellow eye from collateral radiation exposure also needs to be determined.

Neovascular AMD is a heterogenous disease with variation in CNV composition and disease presentation. Differences in lesion composition, size and time in the natural history at presentation may be a source of variability when assessing treatment outcome among the different trials. Evidence from the TAP (TAP Study 1999) and VIP (Bressler 2002) trials showed that many people with minimally classic (less than 50% classic) and occult with no classic lesions had relatively good natural history. Despite presenting as large lesions, they maintained reasonably good visual acuity throughout 24 months follow up without treatment. In contrast, the majority of predominantly classic (more than 50% classic) lesions were four disc areas or less and were more likely to present with lower visual acuity.

Kobayashi 2000 found a significant treatment benefit in participants with smaller CNV (less than 1.5 mm^2) with regard to smaller increase in lesion size and significantly smaller decrease in LogMAR visual acuity for over two years. They also found that there was no significant difference in visual outcome in participants with larger CNV (more than 1.5 mm^2). In contrast, Marcus 2001 did not find lesion size (less than one to more than six disc areas) determined treatment outcome. When the composition of the lesion was considered, Bergink 1998 and Kobayashi 2000 found a better treatment outcome for occult lesions. SFRADS 2002 suggested that one possible reason for the negative outcome in their trial was the predominance of wholly classic and predominantly classic subgroups. This finding was not supported by the other trials included in this review.

The value of radiotherapy in the treatment of neovascular AMD must be considered against other therapeutic options that are available. The present treatment of choice for predominantly classic CNV is photodynamic therapy (PDT) with verteporfin. Alternatives to PDT may have value in the treatment of lesions that are not responsive to PDT. If radiotherapy, with its potential risk of systemic morbidity and exposure to the fellow eye, is to be used as a treatment it needs to be considered against other modalities which do not carry the same risks.

AUTHORS' CONCLUSIONS

Implications for practice

Considerable clinical and statistical heterogeneity between published trials of radiotherapy for AMD mean that we cannot draw any conclusions as to treatment effect. It is possible that a moderate treatment benefit from radiotherapy exists. The results of this review do not currently support a role for external beam radiotherapy in people with neovascular AMD.

Implications for research

Future trials should have a sufficient sample size to detect moderate effects and should report data on visual acuity outcomes so as to enable their inclusion in systematic overviews. Consistent reporting of data on factors such as lesion size and composition would also facilitate synthesis. Adequate masking of the treatment groups should be considered a priority. It is possible that radiotherapy may have a role as adjunctive treatment in conjunction with anticipated pharmacological treatments. However, given the recent evidence that most lesions are amenable to treatment with PDT if identified at a smaller lesion size, trials evaluating radiotherapy against PDT are warranted before radiotherapy can be widely used.

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REFERENCES

References to studies included in this review

Anders 1998 *{published data only}*

Anders N, Stahl H, Dorn A, Walkow T, Hosten N, Wust P, et al.Radiotherapy of exudative senile macular degeneration. A prospective controlled study [Strahlentherapie der exsudativen altersabhangigen Makuladegeneration. Eine prospektive kontrollierte Studie]. *Ophthalmologe* 1998;**95**: 760–4.

Bergink 1998 *{published data only}*

* Bergink GJ, Hoyng CB, Van der Maazen RW, Vingerling JR, van Daal WA, Deutman AF. A randomised controlled trial of efficacy of radiation therapy in the control of subfoveal neovascularisation in age-related macular degeneration: radiation verses observation. *Graefe's Archive for Clinical and Experimental Ophthalmology* 1998;**236**(5): 321–5.

Hoyng CB, Tromp AI, Meulendijks CFM, Leys A, van der Maazen RWM, Deutman AF, et al.Side effects after radiotherapy of age-related macular degeneration with the Nijmegen technique. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2002;**240**:337–41.

Char 1999 *{published data only}*

Char DH, Irvine AI, Posner MD, Quivey J, Phillips TL, Kroll S. Randomised trial of radiation for age-related macular degeneration. *American Journal of Ophthalmology* 1999;**127**:574–8.

Ciulla 2002 *{published data only}*

Ciulla TA, Danis RP, Klein SB, Malinovsky VE, Soni PS, Pratt LM, et al.Proton therapy for exudative age-related macular degeneration: a randomized, sham-controlled clinical trial. *American Journal of Ophthalmology* 2002;**134**: 905–6.

Eter 2002 *{published data only}*

Eter N, Schuller H, Spitznas M. Radiotherapy for age-related macular degeneration: is there a benefit for classic CNV. *International Ophthalmology* 2002;**24**:13–9.

Kacperek 2001 *{published data only}*

Kacperek A, Briggs M, Sheen M, Damato BE, Errington RD, Harding S. Macular degeneration treatment at Clatterbridge Centre for oncology: treatment and preliminary results. *Physica Medica* 2001;**17**(Suppl 3):7–9.

Kobayashi 2000 *{published data only}*

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

Marcus 2001 *{published data only}*

Marcus DM, Camp MW, Sheils WC, McIntosh SB, Leibach DB, Johnson MH, et al.Sham radiation in clinical trials assessing radiotherapy for exudative age-related macular degeneration. *Retina* 1999;**19**:525–30.

Marcus DM, Sheils C, Johnson MH, McIntosh SB, Leibach DB, Maguire A, et al.External beam irradiation of subfoveal choroidal neovascularisation complicating age-related macular degeneration. *Archives of Ophthalmology* 2001;**1** (19):171–80.

RAD 1999 *{published data only}*

* The Radiation Therapy for Age-Related Macular Degeneration (RAD) Group. A prospective, randomised, double-masked trial on radiation therapy for neovascular age-related macular degeneration. *Ophthalmology* 1999; **106**:2239–47.

Vacha P, Debus J, Wiegel T, Schuchardt U, Schaefer U, Engenhart-Cabillic R. A prospective randomized, double-blind multicenter-trial on radiation therapy for neovascular age-related macular degeneration (armd) [abstract]. *European Journal of Cancer* 2001;**37**:275 A1015.

SFRADS 2002 *{published data only}*

Hart PM, Chakravarthy U, Mackenzie G, Chisholm IH, Bird AC, Stevenson MR, 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 2002 *{published data only}*

Valmaggia C, Ries G, Ballinari P. A 5-year follow-up study for distance visual acuity after low dose radiation on subfoveal choroidal neovascularization in age-related macular degeneration. *Documenta Ophthalmologica* 2001; **103**:201–9.

* 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.

References to studies excluded from this review

Bergink 1995 *{published data only}*

Bergink GJ, Deutman AF, Van Den Broek JECM, Van Daal WAJ, Van Der Maazen RMW. Radiation therapy for age-related subfoveal choroidal neovascular membranes. *Documenta Ophthalmologica* 1995;**90**:67–74.

Brown 1997 *{published data only}*

Brown GC, Freire JE, Vander J, Brady LW, Shields CL, Shields JA, et al.Strontium-90 brachytherapy for exudative, age related macular degeneration: a pilot study [abstract]. *International Journal of Radiation Oncology, Biology, Physics* 1997;**39**:332 A2184.

Eter 2001 *{published data only}*

Eter N, Schuller H. External beam radiotherapy for age-related macular degeneration causes transient objective changes in tear-film function. *Graefe's Archive of Clinical and Experimental Ophthalmology* 2001;**239**:923–6.

Honjo 1997 *{published data only}*

Honjo M, Mandai M, Hiroshiba N, Miyamoto H, Takahashi M, Ogura Y, et al.Evaluation of the early-phase response of neovascular membrane in age-related macular degeneration to low-dose radiation. *Japanese Journal of Clinical Ophthalmology* 1997;**51**:1563–9.

Mandai 1998 *{published data only}*
Mandai M, Takahashi M, Miyamoto H, Hiroshiba N, Kimura H, Ogura Y, et al.Longterm effects of radiation treatment for age-related macular degeneration. *Japanese Journal of Clinical Ophthalmology* 1998;**52**:567–71.

Mandai 2000 *{published data only}*
Mandai M, Takahashi M, Miyamoto H, Hiroshiba N, Kimura H, Ogura Y, et al.Long-term outcome after radiation therapy for subfoveal choroidal neovascularization associated with age-related macular degeneration. *Japanese Journal of Ophthalmology* 2000;**44**:530–7.

Matsuhashi *{published data only}*
Matsuhashi H, Noda Y, Takahashi D, Mariya Y. Radiation therapy for small choroidal neovascularization in age-related macular degeneration. *Japanese Journal of Ophthalmology* 2000;**44**:653–60.

Matsuhashi 1996 *{published data only}*
Matsuhashi H, Takahashi D, Noda Y, Mariya Y, Tarusawa N, Yoshimoto H, et al.Low-dose radiation, therapy for choroidal neovascularization in age-related macular degeneration. *Nippon Ganka Gakkai Zasshi* 1996;**100**: 803–9.

Postgens 1997 *{published data only}*
Postgens H, Bodanowitz S, Kroll P. Low-dose radiation therapy for age-related macular degeneration. *Graefe's Archive of Clinical and Experimental Ophthalmology* 1997; **235**:656–61.

Saric 2001 *{published data only}*
Saric B, Sikic J, Katusic D, Vukojevic N. Brachytherapy - optional treatment for choroidal neovascularization secondary to age-related macular degeneration. *Collegium Antropologicum* 2001;**25 Suppl**:89–96.

Taniguchi 1996 *{published data only}*
Taniguchi T, Mandai M, Honjo M, Matsuda N, Miyamoto H, Takahashi M, et al.Radiation treatment for age-related macular degeneration. *Japanese Journal of Clinical Ophthalmology* 1996;**50**:1821–6.

Tholen 2000 *{published data only}*
* Tholen AM, Meister A, Bernasconi PP, Messmer EP. Radiotherapy for choroidal neovascularization (CNV) in age-related macular degeneration (AMD) [Radiotherapie von choroidalen Neovaskularisationen (CNV) bei altersabhangiger Makuladegeneration (AMD)]. *Klinische Monatsblatter fur Augenheilkunde* 2000;**216**:112–5.
Tholen AM, Meister A, Bernasconi PP, Messmer EP. Radiotherapy for choroidal neovascularization in age-related macular degeneration. A pilot study using low- versus high-dose photon beam radiation [Radiotherapie von subretinalen Neovaskularisationsmembranen bei altersabhangiger Makuladegeneration (AMD). Niedrig– versus hochdosierte Photonenbestrahlung]. *Ophthalmologe* 1998;**95**:691–8.

References to studies awaiting assessment

Anon 2003 *{published data only}*
Anonymous. The results of randomized controlled trial of low-dose radiation for wet-type age-related macular degeneration on a 1-year term basis. *Nippon Ganka Gakkai Zasshi* 2003;**107**:326–30.

Additional references

Alderson 2004
Alderson P, Green S, Higgins JPT, editors. Cochrane Reviewers' Handbook 4.2.2 [updated March 2004]. In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Altman 2003
Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;**326**:219.

Bressler 2001
Bressler NM. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. *Archives of Ophthalmolology* 2001;**119**: 198–207.

Bressler 2002
Bressler NM. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization. Verteporfin in photodynamic therapy report 2. *Ophthalmology* 2002;**133**:168–9.

Evans 1995
Evans JR. Causes of blindness and partial sight in England and Wales 1990-1991. *Studies on Medical and Population Subjects*. Vol. **57**, London: HMSO, 1995.

Evans 2001
Evans JR. Risk factors for age-related macular degeneration. *Progress in Retinal and Eye Research* 2001;**20**(2):227–53.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**: 557–60.

MPSG 1994
Macular Photocoagulation Study Group. Laser photocoagulation for juxtafoveal choroidal neovascularization. Five-year results from randomized clinical trials. Macular Photocoagulation Study Group. *Archives of Ophthalmology* 1994;**112**(4):500–9.

TAP Study 1999
TAP Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials - TAP report. *Archives of Ophthalmology* 1999;**117**(10):1329–45.

Wormald 2004
Wormald R, Evans J, Smeeth L, Henshaw K. Photodynamic therapy for neovascular age-related macular degeneration.

Cochrane Database of Systematic Reviews 2004, Issue 3.
[DOI: 10.1002/14651858.CD002030.pub3]
* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anders 1998

Methods	Single centre. Allocation: not stated. Masking: participant - no; provider - no; outcome - no. Exclusions after randomisation: not stated
Participants	Country: Germany. Number randomised: 76. Mean age: 77.7. Sex: 67% women. Inclusion Criteria: 50+ years; visual acuity decrease (0.05 and 0.5); angiographically proven CNV. Exclusion criteria: previous laser photocoagulation to macula; previous radiation; other eye disease
Interventions	Treatment: 12 Gy (6 x 2 Gy). Control: observation. Duration: 8 days
Outcomes	Visual acuity, near and distance; FFA.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bergink 1998

Methods	Single centre. Allocation: not stated. Masking: participant - no; provider - no; outcome - no. Exclusions after randomisation: 3.
Participants	Country: Netherlands. Number randomised: 74. Mean age: 74. Sex: 56% women. Inclusion criteria: 55+ years; visual acuity 20/200 or better; angiographically proven CNV; clinical signs of ARM; informed consent. Exclusion criteria: previous laser photocoagulation to macula; radiation for ear nose and throat or brain disease; diabetes

Bergink 1998 (*Continued*)

Interventions	Treatment: 24 Gy (4 x 6 Gy). Control: observation. Duration: 21 days.
Outcomes	Visual acuity (Snellen); Doubling of CNV size (FFA).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Char 1999

Methods	Single centre. Allocation: not stated. Masking: participant - no; provider - no; outcome - unclear (yes for FFA). Exclusions after randomisation: not stated
Participants	Country: USA. Number randomised: 27. Mean age: 76. Sex: 52% women. Inclusion criteria: Subfoveal CNV secondary to AMD with visual acuity less than 20/40. Exclusion criteria:
Interventions	Treatment: 7.5 Gy. Control: observation. Duration: one day
Outcomes	Visual acuity (ETDRS chart).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ciulla 2002

Methods	Single centre. Allocation: not stated. Masking: participant - yes; provider - yes; outcome - yes. Exclusions after randomisation: not stated
Participants	Country: USA. Number randomised: 37. Median age: 71. Sex: 38% women. Inclusion criteria: Subfoveal CNV due to AMD; visual impairment of affected eye less than 6 months duration; best-corrected VA of affected eye < = 20/40 and > = 20/400. Exclusion criteria: Unable to maintain steady fixation; preexisting retinal eye disease or media opacity; no informed consent
Interventions	Treatment: 16 Gy (2 x 8 Gy). Control: sham irradiation (not described). Duration: 2 days
Outcomes	Visual acuity (ETDRS chart).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Eter 2002

Methods	Multicentre: 3 centres. Allocation: central telephone; blocked by centre. Masking: participant: no; provider: no; outcome: no. Exclusions after randomisation: 3 treatment, 1 control
Participants	Country: Germany. Number randomised: 45. Median age: 74. Sex: 53% women. Inclusion criteria: age 45+ years; classic/occult CNV; informed consent; no prior radiation treatment to head; no vascular eye disease; no prior treatment of AMD. Exclusion criteria:
Interventions	Treatment: 20 Gy (10 x 2 Gy). Control: observation. Duration: one week
Outcomes	Visual acuity (logarithmic chart).

Eter 2002 (*Continued*)

Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kacperek 2001

Methods	Single centre. Allocation: unclear. Masking: participant - no; provider - no; outcome - no. Exclusions after randomisation: not stated
Participants	Country: UK. Number randomised: 66. Mean age: 76 years. Sex: Inclusion criteria: Aged 50+ with subfoveal CNV (classic) and evidence of AMD e.g. drusen, VA>6/60. Exclusion criteria: diabetes, severe hypertension and retinal vascular disease, myopia
Interventions	Treatment: 18 Gy (4 x 4.5 Gy). Control: observation. Duration:4 days
Outcomes	Visual acuity
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kobayashi 2000

Methods	Single centre. Allocation: computer generated. Masking: participant - no; provider - yes; outcome - unclear (yes for FFA). Exclusions after randomisation: not stated

Kobayashi 2000 (*Continued*)

Participants	Country: Japan. Number randomised: 101. Mean age: 72. Sex: 64% female. Inclusion criteria: 60+ years; unsuitability for laser under macular photocoagulation criteria; three or less months of new or progressive CNV; visual acuity 20/50 or worse. Exclusion criteria: pre-existing ocular disease (glaucoma, severe myopia, chronic inflammation, neoplasia) ; diabetes; uncontrolled hypertension; known life-threatening disease
Interventions	Treatment: 20 Gy (10 x 2 Gy). Control: observation. Duration: 14 days.
Outcomes	Visual acuity (ETDRS); area of CNV (FFA); safety.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Marcus 2001

Methods	Single centre. Allocation: computer generated; blocked. Masking: participant - yes; provider - yes; outcome - yes. Exclusions after randomisation: not stated
Participants	Country: USA. Number randomised: 83. Mean age: 76. Sex: 61% female. Inclusion criteria: active subfoveal CNV secondary AMD; >48 years of age; visual acuity > / = 20/400; clinical and angiographic evidence of a choroidal neovascular membrane, which is itself or its contiguous blood involving the centre of the foveal avascular zone. Exclusion criteria: previous laser treatment; choroidal neovascularisation due to other causes; retinal vascular diseases e.g. diabetes; previous ocular, orbital or periorbital radiation; likely candidates for chemotherapeutic agents
Interventions	Treatment: 14 Gy (7 x 2 Gy). Control: 1 sham treatment. Duration: 7 working days.
Outcomes	Visual acuity (ETDRS); contrast sensitivity; appearance of fundus (FFA and photography)

Marcus 2001 (*Continued*)

Notes	Patients with subfoveal choroidal neovascular membranes who were eligible for subfoveal laser according to macular photocoagulation study guidelines were offered laser versus radiation or observation versus radiation (this study)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

RAD 1999

Methods	Multicentre: 9 centres. Allocation: computer generated. Masking: participant - yes; provider - yes; outcome - yes. Exclusions after randomisation:
Participants	Country: Germany. Number randomised: 205. Mean age: 74. Sex: 60% female. Inclusion criteria: 50+ years old; written informed consent; exudative AMD with subfoveal involvement and signs of ARM in the fellow eye; CNV 6+ disc diameters in size; visual acuity 20/320 or better in study eye; symptoms for six months or less. Exclusion criteria: ocular disease that could compromise the visual acuity in the study eye; haemorrhage; previous macular photocoagulation or PDT; history of antiangiogenic drugs
Interventions	Treatment: 16 Gy (8 x 2 Gy). Control: 8 x 0 Gy. Duration: 10 days.
Outcomes	Visual acuity (ETDRS); FFA and fundus photography.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

SFRADS 2002

Methods	Multicentre: 3 centres. Allocation: central telephone; blocked by centre. Masking: participant: no; provider: no; outcome: yes. Exclusions after randomisation: 3 treatment, 1 control
Participants	Country: UK. Number randomised: 203. Mean age: 75. Sex: 57% female. Inclusion criteria: Aged 60+; subfoveal CNV; 20/200 or better in study eye. Exclusion criteria: Inability to give informed consent; late leakage of indeterminate origin; blood under geometric centre of the fovea; other ocular disease; diabetes; other trials; prior radiotherapy
Interventions	Treatment: 12 Gy (6 X 2 Gy). Control: observation. Duration:
Outcomes	Visual acuity (ETDRS chart); near vision (Bailey-Lovie chart); radiation-associated problems
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Valmaggia 2002

Methods	Single centre. Allocation: not stated. Masking: participant - yes; provider - yes; outcome - yes. Exclusions after randomisation: no stated
Participants	Country: Switzerland. Number randomised: 161. Mean age - 75. Sex: 58% female. Inclusion criteria: Symptoms of reduced vision, central central scotoma or metamorphopsia. Exclusion criteria: foveal haemorrhage; severe haemorrhage impeding measurement of CNV; PED; other ocular disease (glaucoma, severe myopia, diabetic retinopathy)
Interventions	Treatment: 8 Gy (4 X 2 Gy) or 16 Gy (4 X 4 Gy). Control: 1 Gy (4 X 0.25 Gy). Duration: 4 days.

Valmaggia 2002 (*Continued*)

Outcomes	Visual acuity (logMAR chart); reading ability; CNV size (FFA/indocyanine green); radiation-associated side effects (ocular irritation, conjunctivitis, cataract, radiation retinopathy, radiation optic neuropathy)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Abbreviations:
AMD - age-related macular degeneration
ARM - age-related maculopathy
CNV - choroidal neovascularisation
ETDRS - Early Treatment of Diabetic Retinopathy Study
FFA - fundus fluorescein angiography
Gy - gray
PDT - photodynamic therapy
PED - pigment epithelial detachment

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bergink 1995	Treatment groups probably not randomly allocated.
Brown 1997	Treatment groups allocated sequentially.
Eter 2001	One eye treated and fellow eye served as a control. Unclear whether first eye treated randomly
Honjo 1997	Treatment groups probably not randomly allocated.
Mandai 1998	Treatment groups probably not randomly allocated.
Mandai 2000	Retrospective study - groups not allocated randomly.
Matsuhashi	Treatment groups not allocated randomly. Control group consisted of people who had refused radiation or laser treatment
Matsuhashi 1996	Treatment groups not allocated randomly
Postgens 1997	Retrospective study - groups not allocated randomly.

(*Continued*)

Saric 2001	Control group consisted of patients who had refused treatment
Taniguchi 1996	Treatment and control groups probably not randomly allocated
Tholen 2000	This study initially began as an RCT but the trial was stopped because of radiogenic complications in the high dose group (36Gy). The study was continued as a non-randomised study and the reports did not distinguish randomised and non-randomised comparisons