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Radiotherapy for neovascular age-related macular degeneration (Review)

Evans JR, Igwe C, Jackson TL, Chong V

Evans JR, Igwe C, Jackson TL, Chong V.
Radiotherapy for neovascular age-related macular degeneration.
Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004004.
DOI: 10.1002/14651858.CD004004.pub4.

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[Intervention Review]

Radiotherapy for neovascular age-related macular degeneration

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Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 8, 2020.

Citation: Evans JR, Igwe C, Jackson TL, Chong V. Radiotherapy for neovascular age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2020, Issue 8. Art. No.: CD004004. DOI: 10.1002/14651858.CD004004.pub4.

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ABSTRACT

Background

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

Objectives

To examine the effects of radiotherapy on neovascular AMD.

Search methods

We searched CENTRAL, MEDLINE, Embase, LILACS and three trials registers and checked references of included studies. We last searched the databases on 4 May 2020.

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 choroidal neovascularisation (CNV) secondary to AMD.

Data collection and analysis

We used standard procedures expected by Cochrane. We graded the certainty of the evidence using GRADE. We considered the following outcomes at 12 months: best-corrected visual acuity (BCVA) (loss of 3 or more lines, change in visual acuity), contrast sensitivity, new vessel growth, quality of life and adverse effects at any time point.

Main results

We included 18 studies (n = 2430 people, 2432 eyes) of radiation therapy with dosages ranging from 7.5 to 24 Gy. These studies mainly took place in Europe and North America but two studies were from Japan and one multicentre study included sites in South America. Three of these studies investigated brachytherapy (plaque and epimacular), the rest were studies of external beam radiotherapy (EBM) including one trial of stereotactic radiotherapy. Four studies compared radiotherapy combined with anti-vascular endothelial growth factor (anti-VEGF) with anti-VEGF alone. Eleven studies gave no radiotherapy treatment to the control group; five studies used sham irradiation; and one study used very low-dose irradiation (1 Gy). One study used a mixture of sham irradiation and no treatment. Fifteen studies were judged to be at high risk of bias in one or more domains.

Radiotherapy versus no radiotherapy

There may be little or no difference in loss of 3 lines of vision at 12 months in eyes treated with radiotherapy compared with no radiotherapy (risk ratio (RR) 0.82, 95% confidence interval (CI) 0.64 to 1.04, 811 eyes, 8 studies, I^2 = 66%, low-certainty evidence). Low-certainty

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evidence suggests a small benefit in change in visual acuity (mean difference (MD) -0.10 logMAR, 95% CI -0.17 to -0.03; eyes = 883; studies = 10) and average contrast sensitivity at 12 months (MD 0.15 log units, 95% CI 0.05 to 0.25; eyes = 267; studies = 2). Growth of new vessels (largely change in CNV size) was variably reported and It was not possible to produce a summary estimate of this outcome. The studies were small with imprecise estimates and there was no consistent pattern to the study results (very low-certainty evidence). Quality of life was only reported in one study of 199 people; there was no clear difference between treatment and control groups (low-certainty evidence). Low-certainty evidence was available on adverse effects from eight of 14 studies. Seven studies reported on radiation retinopathy and/or neuropathy. Five of these studies reported no radiation-associated adverse effects. One study of 88 eyes reported one case of possible radiation retinopathy. One study of 74 eyes graded retinal abnormalities in some detail and found that 72% of participants who had radiation compared with 71% of participants in the control group had retinal abnormalities resembling radiation retinopathy or choroidopathy. Four studies reported cataract surgery or progression: events were generally few with no consistent evidence of any increased occurrence in the radiation group. One study noted transient disturbance of the precorneal tear film but there was no evidence from the other two studies that reported dry eye of any increased risk with radiation therapy. None of the participants received anti-VEGF injections.

Radiotherapy combined with anti-VEGF versus anti-VEGF alone

People receiving radiotherapy/anti-VEGF were probably more likely to lose 3 or more lines of BCVA at 12 months compared with anti-VEGF alone (RR 2.11, 95% CI 1.40 to 3.17, 1050 eyes, 3 studies, moderate-certainty). Most of the data for this outcome come from two studies of epimacular brachytherapy (114 events) compared with 20 events from the one trial of EBM. Data on change in BCVA were heterogenous (I^2 = 82%). Individual study results ranged from a small difference of -0.03 logMAR in favour of radiotherapy/anti-VEGF to a difference of 0.13 logMAR in favour of anti-VEGF alone (low-certainty evidence). The effect differed depending on how the radiotherapy was delivered (test for interaction P = 0.0007). Epimacular brachytherapy was associated with worse visual outcomes (MD 0.10 logMAR, 95% CI 0.05 to 0.15, 820 eyes, 2 studies) compared with EBM (MD -0.03 logMAR, 95% CI -0.09 to 0.03, 252 eyes, 2 studies). None of the included studies reported contrast sensitivity or quality of life. Growth of new vessels (largely change in CNV size) was variably reported in three studies (803 eyes). It was not possible to produce a summary estimate and there was no consistent pattern to the study results (very low-certainty evidence). For adverse outcomes, variable results were reported in the four studies. In three studies reports of adverse events were low and no radiation-associated adverse events were reported. In one study of epimacular brachytherapy there was a higher proportion of ocular adverse events (54%) compared to the anti-VEGF alone (18%). The majority of these adverse events were cataract. Overall 5% of the treatment group had radiation device-related adverse events (17 cases); 10 of these cases were radiation retinopathy. There were differences in average number of injections given between the four studies (1072 eyes). In three of the four studies, the anti-VEGF alone group on average received more injections (moderate-certainty evidence).

Authors' conclusions

The evidence is uncertain regarding the use of radiotherapy for neovascular AMD. Most studies took place before the routine use of anti-VEGF, and before the development of modern radiotherapy techniques such as stereotactic radiotherapy. Visual outcomes with epimacular brachytherapy are likely to be worse, with an increased risk of adverse events, probably related to vitrectomy. The role of stereotactic radiotherapy combined with anti-VEGF is currently uncertain. Further research on radiotherapy for neovascular AMD may not be justified until current ongoing studies have reported their results.

PLAIN LANGUAGE SUMMARY

How effective is radiotherapy for treating wet age-related macular degeneration (AMD) (a degenerative eye condition)?

Why this question is important

AMD is a common condition of the eyes that may develop in people aged over 50. It affects the central area (macula) of the back of the eye (retina). First, yellow spots (drusen) develop under the retina. These can been seen by health professionals during examinations of the eyes. As AMD progresses, new blood vessels can grow in the macula. These vessels may bleed or cause scarring; this is called 'neovascular' or 'wet' AMD. Wet AMD can cause people to lose the central part of their vision.

There is no cure for wet AMD. However, there are treatments designed to stop vision from worsening. One such treatment is radiotherapy (using radiation to kill harmful cells). To find out how effective radiotherapy is for treating wet AMD and whether it causes unwanted effects, we reviewed the evidence from research studies.

How we identified and assessed the evidence

First, we searched for all relevant studies in the medical literature. We then compared the results, and summarized the evidence from all the studies. Finally, we assessed how certain the evidence was. We considered factors such as the way studies were conducted, study sizes, and consistency of findings across studies. Based on our assessments, we categorized the evidence as being of very low-, low-, moderate- or high-certainty.

What we found

We identified 18 relevant studies on a total of 2340 people with wet AMD. These studies mainly took place in Europe and North America, though two studies were from Japan and one study included sites in South America. Fifteen studies investigated external beam

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radiotherapy and three studies investigated internal radiotherapy (brachytherapy), where radioactive materials are placed on the surface of the eye.

Studies compared:

radiotherapy alone with no radiotherapy or a sham treatment (14 studies,1223 people); or

radiotherapy plus eye injections (of a medicine called anti-vascular endothelial growth factor (VEGF)) with eye injections only (four studies,1117 people); or

The studies showed that:

When radiotherapy was compared with no radiotherapy or a sham treatment, at 12-month follow-up

There may be little difference in how likely people's vision is to worsen by 3 lines or more on a vision chart (low-certainty).

There may be a small difference in average visual sharpness (in the order of 1 line of a vision chart) favouring radiotherapy (low-certainty).

People's ability to distinguish between bright and dim parts of an image may be slightly better with radiotherapy (low-certainty).

The evidence on growth of new blood vessels in the back of the eye was inconsistent (very low-certainty).

There may be little difference in quality of life (low-certainty).

Studies that recorded unwanted effects generally reported no radiation-associated damage to the retina or optical nerve. Other unwanted effects, such as cataracts, were uncommon. There was no consistent evidence that unwanted effects were more likely in the radiation group (low-certainty).

When radiotherapy combined with anti-VEGF was compared with anti-VEGF alone, 12 months follow-up

People treated with radiotherapy plus anti-VEGF are probably twice as likely to lose 3 lines or more on a vision chart than people treated with anti-VEGF alone (moderate-certainty).

Studies reported inconsistent results on average vision sharpness (low-certainty) and new vessel growth (very low-certainty evidence). Average vision sharpness may be worse with brachytherapy.

No studies investigated the impact on people's ability to distinguish between bright and dim parts of an image, or quality of life.

Three out of four studies reported few unwanted effects and no radiation-associated damage to the retina or optical nerve. In one study, half of the people treated with brachytherapy reported unwanted effects (particularly cataracts) and there were some instances of damage to the retina caused by the brachytherapy (low-certainty).

In three out of four studies, people treated with radiotherapy received fewer anti-VEGF injections (moderate-certainty).

Conclusion
It is uncertain whether radiotherapy on its own or with eye injections of anti-VEGF is effective for treating wet AMD.

How up-to-date is this review?
Cochrane researchers searched for studies that had been published up to 4 May 2020.

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SUMMARY OF FINDINGS

Summary of findings 1. Radiotherapy versus control for neovascular AMD

Radiotherapy versus control for neovascular AMD

Patient or population: people with neovascular AMD
Settings: eye hospital
Intervention: radiation therapy

Comparator: control (no treatment or sham irradiation)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of people or eyes (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with radiotherapy				
Loss of 3 or more lines of best-corrected visual acuity Measured using a logMAR chart Follow-up: 12 months	550 per 1,000	451 per 1,000 (352 to 666)	RR 0.82 (0.64 to 1.04)	811 eyes (8 RCTs)	⊕⊕⊖⊖ **low** [1]	At 24 months, RR 0.78 (0.63 to 0.97), 654 eyes (4 RCTs) I^2 = 73%
Change in best corrected visual acuity (logMAR units) Measured using a logMAR chart. Lower scores represent better visual acuity Follow-up: 12 months	Change in visual acuity in control group ranged from -0.339 to 0.395 logMAR units.	The mean difference in visual acuity in the intervention groups was -**0.10 logMAR units (better)** (-0.17 to -0.03)	-	883 eyes (10 RCTs)	⊕⊕⊖⊖ **low** [2]	At 24 months, the mean difference in change visual acuity in the radiotherapy group was -**0.09 logMAR units (better)** (-0.15 to -0.03) compared with control, 516 eyes (6 RCTs)
Contrast sensitivity (log contrast threshold) Measured using a Pelli-Robson chart. Higher scores represent better contrast sensitivity.	One trial reported change in control group of 0.39 log units	The mean difference was **0.15 more log units (better)** (0.05 to 0.25)		267 eyes (2 RCTs)	⊕⊕⊖⊖ **low** [3]	At 24 months, MD 0.11 log-units, (0.00 to 0.22) compared with

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Follow-up: 12 months			control, 257 eyes (2 RCTs)
New vessel growth Measured using fluorescein angiography or fundus photographs Follow-up: 12 months	It was not possible to produce a summary estimate due to variable reporting of this outcome. The studies were small with imprecise estimates and there was no consistent pattern to the study results.	(9 RCTs)	⊕⊖⊖⊖ **very low** 4
Quality of life Follow-up: 12 months	Mean change in scores on four dimensions of Daily Living Tasks Dependent on Vision were similar in radiotherapy and control groups. Mean differences ranged from -2.80 (-8.89 to 3.29) to 1.20 (-7.53 to 9.93).	199 people (1 RCT)	⊕⊕⊖⊖ **low** [5]
Any adverse outcome Follow-up: any time point	Six out of 14 studies did not report on adverse effects. Seven studies reported on radiation retinopathy and/or neuropathy. Five of these studies reported no radiation-associated adverse effects. One study of 88 eyes reported one case of possible radiation retinopathy. One study of 74 eyes graded retinal abnormalities in some detail and found that 72% of participants who had radiation compared with 71% of participants in the control group had retinal abnormalities resembling radiation retinopathy or choroidopathy. Four studies reported cataract surgery or progression: events were generally low and no consistent evidence of any increased occurrence in the radiation group. One study noted transient disturbance of the precorneal tear film but no evidence from the other 2 studies that reported dry eye of any increased risk with radiation therapy.	881 eyes (8 RCTs)	⊕⊕⊖⊖ **low** [6]
Number of anti-VEGF injections	Not relevant to this comparison	-	-

*The **risk with control** was estimated from the pooled risk in the control groups of the included studies. The **risk with radiotherapy** (and its 95% confidence interval) is based on the risk in the control group and the**relative effect** of the intervention (and its 95% CI).
AMD: age-related macular degeneration **Anti-VEGF:** anti-vascular endothelial growth factor **CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level for risk of bias (6 of the 8 studies were high risk of bias in one or more domain) and downgraded one level for inconsistency (individual study effect estimates ranged from 0.42 to 1.22, $I^2 = 66\%$). We did not downgrade an additional level for imprecision, even though the confidence intervals include 1 (no difference), because we had already downgraded for inconsistency which will have contributed to the imprecision of the pooled estimate.

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[2] Downgraded one level for risk of bias (8 of the 10 studies were high risk of bias in one or more domain); and downgraded one level for publication bias as there was an asymmetric funnel plot indicating possible publication bias.
[3] Downgraded one level for risk of bias (both studies were high risk of bias in one or more domains); and downgraded one level for imprecision (the upper confidence interval was close to 0, no difference).
[4]Downgraded one level for risk of bias (8 out of the 9 studies were high risk of bias in one or more domain); downgraded one level for imprecision (the individual studies were small with imprecise estimates); and downgraded one level for inconsistency (there was no consistent pattern to the individual study results)
[5] Downgraded one level for risk of bias study (study was not masked); and downgraded one level for imprecision (confidence intervals include 0).
[6]Downgraded one level for risk of bias (8 out of the 9 studies were high risk of bias in one or more domain); downgraded one level for imprecision (the individual studies were small with imprecise estimates).

Summary of findings 2. Radiotherapy combined with anti-VEGF versus anti-VEGF alone for neovascular AMD

Radiotherapy combined with anti-VEGF versus anti-VEGF alone for neovascular AMD

Patient or population: people with neovascular AMD
Settings: eye hospital
Intervention: radiation therapy (external beam or brachytherapy) combined with anti-VEGF (ranibizumab or bevacizumab)

Comparator: anti-VEGF alone (ranibizumab or bevacizumab)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of people or eyes (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with anti-VEGF	Risk with radiotherapy combined with anti-VEGF				
Loss of 3 or more lines of best-corrected visual acuity Measured using a logMAR chart Follow-up: 12 months	70 per 1,000	148 per 1,000 (98 to 222)	RR 2.11 (1.40 to 3.17)	1050 eyes (3 RCTs)	⊕⊕⊕⊖ **moderate**[1]	At 24 months, RR 2.39 (1.68, 3.39), 820 eyes (2 RCTs)
Change in best corrected visual acuity (logMAR units) Measured using a logMAR chart. Lower scores represent better visual acuity Follow-up: 12 months	We did not pool study results because of substantial heterogeneity. Individual study results ranged from a small mean difference of -0.03 logMAR in favour of radiotherapy combined with anti-VEGF to a mean difference of 0.13 logMAR in favour of anti-VEGF alone (I^2 = 82%). There was evidence of a difference in effect depending on how the radiotherapy was delivered(test for interaction P=0.0007). Epimacular brachytherapy was associated with worse visual outcomes (MD 0.10 logMAR, 95% CI 0.05 to 0.15, 2 studies, 820 eyes) compared with external beam radiotherapy (MD -0.03logMAR, 95% CI -0.09 to 0.03, 252 eyes).			1072 eyes (4 RCTs)	⊕⊕⊖⊖ **low** [2]	At 24 months, the mean difference in change visual acuity in the radiotherapy with anti-VEGF group

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			was **0.17 logMAR (worse)** (CI 0.11 to 0.23) compared with anti-VEGF alone, 819 eyes, 2 RCTs of epimacular brachytherapy
Contrast sensitivity (log contrast threshold) Measured using a Pelli-Robson chart. Higher scores represent better contrast sensitivity. Follow-up: 12 months	None of the included studies reported this outcome.	-	-
New vessel growth Measured using fluorescein angiography or fundus photographs Follow-up: 12 months	It was not possible to produce a summary estimate due to variable reporting of this outcome. There was no consistent pattern to the individual study results.	803 eyes (3 RCTs)	⊕⊖⊖⊖ **very low**[3]
Quality of life Follow-up: 12 months	None of the included studies reported this outcome.	-	-
Any adverse outcome Follow-up: any time point	Variable results were reported in the 4 studies. In 3 studies reports of adverse events were low and no radiation-associated adverse events reported. In one study of epimacular brachytherapy the radiotherapy and anti-VEGF treatment group had a higher proportion of ocular adverse events (54%) compared to the anti-VEGF alone (18%). The majority of these adverse events were cataract. Overall 5% of the treatment group had radiation device-related adverse events (17 cases); 10 of these cases were radiation retinopathy.	1072 eyes (4 RCTs)	⊕⊕⊖⊖ **low** [6]
Number of anti-VEGF injections	There were some differences in average number of injections. In 3 of the 4 studies, the anti-VEGF alone group on average received more injections	1072 eyes (4 RCTs)	⊕⊕⊕⊖ **moderate**[1]

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*The **risk with control** was estimated from the pooled risk in the control groups of the included studies. The **risk with radiotherapy** (and its 95% confidence interval) is based on the risk in the control group and the**relative effect** of the intervention (and its 95% CI).
AMD: age-related macular degeneration **Anti-VEGF:** anti-vascular endothelial growth factor **CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level for risk of bias (2 of the studies were at risk of performance and detection bias).
[2]Downgraded one level for risk of bias (3 of the 4 studies were high risk of bias in one or more domain); and downgraded one level for inconsistency (I^2 = 81%).
[3]Downgraded one level for risk of bias (2 of the studies were at risk of performance and detection bias); downgraded one level for imprecision (2 of the individual studies estimates were imprecise); and downgraded one level for inconsistency (there was no consistent pattern to the individual study results).
[4]Downgraded one level for risk of bias (3 out of the 4 studies were high risk of bias in one or more domain); downgraded one level for inconsistency (different results in the different studies).

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BACKGROUND

Description of the condition

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 higher income countries (Flaxman 2017). 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 (Evans 2012). 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 AMD. 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.

There are two types of AMD: geographic atrophy (large area of atrophy centred in the macula) and choroidal neovascularisation (CNV) also known as wet AMD. This review is concerned with treatment for neovascular AMD.

In neovascular 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 in 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.

Description of the intervention

Radiotherapy is commonly used in oncology and its use is increasing in the treatment of non-neoplastic diseases. 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.

There are two ways of delivering the radiation dose, either by external beam radiotherapy (i.e. from outside the eye) or by brachytherapy whereby the dose is delivered intra-ocularly or transscleral. The original external beam radiation therapy techniques delivered high-energy radiation through the eye and surrounding tissue. More recent modifications of this technique include stereotactic radiotherapy whereby lower doses are applied in a targeted fashion. In epimacular brachytherapy, after vitrectomy the radiation source is applied to the fovea for a short period of time.

How the intervention might work

Clinical experience suggests that cumulative doses of up to 25 Gy seldom cause damage to the retina or optic nerve. Radiation therapy is anti-angiogenic. Radiation targets cells that are dividing. As the endothelial cells in CNV are dividing the hypothesis is that radiotherapy can stop the growth of new blood vessels without significant damage to the retina.

Why it is important to do this review

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

OBJECTIVES

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 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

The outcomes have been amended for the current update: see Differences between protocol and review.

Primary outcomes

The primary outcome for this review was visual acuity. We considered two measures of visual acuity: 3 or more lines best-corrected visual acuity (BCVA) lost on a logMAR chart (equivalent to doubling of visual angle or worse) and change in mean BCVA as a continuous score.

Secondary outcomes

The secondary outcomes for this review were:

- mean change in contrast sensitivity;

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- proportion of people with new vessel growth;
- mean (median) quality of life measured using 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.

In a protocol amendment we added the following outcome:

- number of anti-VEGF injections during the first 12 and 24 months.

Follow up

We measured outcomes at 12 (6 to 18) and 24 (18 to 30) months after radiation treatment.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no restrictions to language or year of publication. The date of the search was 4 May 2020.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 5) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 4 May 2020) (Appendix 1).
- MEDLINE Ovid (1946 to 4 May 2020) (Appendix 2).
- Embase Ovid (1980 to 4 May 2020) (Appendix 3).
- LILACS (Latin American and Caribbean Health Science Information database (1982 to 4 May 2020) (Appendix 4).
- International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com/editAdvancedSearch; searched 4 May 2020) (Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 4 May 2020) (Appendix 6).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 22 May 2019. Update search not run as the database is not available due to Covid 19 resource restrictions) (Appendix 7).

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

Selection of studies

Two review authors independently scanned the titles and abstracts resulting from the searches. We obtained full-text copies of all potentially or definitely relevant articles. Two review authors assessed the full-text copies according to the 'Criteria for considering studies for this review'. We resolved disagreements by discussion.

Data extraction and management

Two review authors independently extracted data using a form developed by Cochrane Eyes and Vision. We resolved discrepancies by discussion. In the original review (Sivagnanavel 2004), one author entered data into RevMan 4.2 using the double data-entry facility to check for errors. For the updates in Review Manager 5 (RevMan 5) (Review Manager 2014), data were entered onto a spreadsheet and cut and pasted into RevMan.

Assessment of risk of bias in included studies

We used Cochrane's tool for assessing risk of bias.

Selection bias

Sequence generation:

- Low risk of bias: Computer generated list, random table, other method of generating random list
- Unclear risk of bias: Not reported how list was generated. Trial may be described as “randomised” but with no further details.
- High risk of bias: Alternate allocation, date of birth, records (these RCTs should be excluded)

Allocation concealment

- Low risk of bias: Central centre (web/telephone access), sealed opaque envelopes
- Unclear risk of bias: Not reported how allocation administered. Trial may be described as “randomised” but with no further details.
- High risk of bias: Investigator involved in treatment allocation or treatment allocation clearly not masked

Performance bias

Masking of participants and personnel

- Low risk of bias: Sham treatment in control group and/or clearly stated that participants and personnel (apart from person applying intervention) not aware of which treatment received
- Unclear risk of bias: Described as “double blind” with no information on who was masked.
- High risk of bias: No information on masking and interventions different

Detection bias

- Low risk of bias: clearly stated that outcome assessors were masked and/or sham irradiation in control group
- Unclear risk of bias: Described as “double blind” with no information on who was masked.
- High risk of bias: No information on masking and interventions different

Attrition bias

- Low risk of bias: Missing data less than 20% (i.e. more than 80% follow-up) and equal follow-up in both groups and no obvious reason why loss to follow-up should be related to outcome
- Unclear risk of bias: Follow-up not reported or missing data >20% (i.e. follow-up <80%) but follow-up equal in both groups
- Follow-up different in each group and/or related to outcome

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Selective outcome reporting

- Low risk of bias: outcomes on protocol or trial registry entry reported
- Unclear risk of bias: no access to protocol or trial registry entry
- High risk of bias: outcomes on protocol or trial registry entry not reported

Measures of treatment effect

We used the mean difference (MD) with 95% confidence intervals (CI) for continuous outcomes (e.g. visual acuity logMAR score) and risk ratio (RR) with 95% CI for dichotomous outcomes (e.g. loss of 3 or more lines of BCVA).

Unit of analysis issues

Most studies randomised participants and then studied one eye per person. One trial (Jaakkola 2005) reported data from 88 eyes in 86 participants. As the numbers of people with both eyes erroneously included in the analysis was small in this study, and it was not possible to extract data for people, this error was ignored and data on eyes used in the analysis. There were no cross-over or cluster RCTs, indeed they would not be expected for this intervention. Two of the studies were three arm studies with two intervention groups of with different doses of radiotherapy. For the purposes of the analysis, we combined the intervention groups using the RevMan calculator.

Dealing with missing data

Our analyses assume that missing data are missing at random.

In previous versions of this review we did sensitivity analyses to look at the effect of missing data (Evans 2010). Under various reasonable assumptions regarding missing data, the percentage change in the pooled estimates was small. We have not repeated these analyses for the current update.

Assessment of heterogeneity

We assessed heterogeneity by looking at the forest plots to see whether the confidence intervals for the estimates of effect overlapped and by looking at the χ^2 and I^2 value.

Assessment of reporting biases

We investigated publication bias by doing a scatter plot of the effect estimates from the individual studies against their standard error. We only did this on analyses that included 10 or more study results. An asymmetric graph may indicate that smaller studies that are not statistically significant have not been published although it also may indicate that the effects of treatment are different in small studies.

We assessed selective outcome reporting using the Cochrane risk of bias tool (Assessment of risk of bias in included studies).

Data synthesis

We used a random-effects model to combine results. When data were sparse and we judged a random-effects model would not provide a robust estimate of effect (for example, if there were three or fewer trials), we used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

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 of interest for subgroup analyses (method of delivery, dosage and type of CNV). In a previous version of this review we identified one additional aspect of study design as being 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 divided the trials into two groups for each factor:

- external beam versus brachytherapy;
- 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.

Sensitivity analysis

We did not conduct any sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings table presenting relative and absolute risks. One author (JE) graded the overall quality of the evidence for each outcome using the GRADE classification (GRADEpro) and the other authors checked this grading. We included the following outcomes at 12 months: loss of 3 or more lines BCVA, change in BCVA, contrast sensitivity, new vessel growth, quality of life, any adverse outcome (any time point), and number of anti-VEGF injections.

RESULTS

Description of studies

Results of the search

The searches conducted in July 2004 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. A total of 11 trials were considered suitable for inclusion in the review (Anders 1998; Bergink 1998; Char 1999; Ciulla 2002; Eter 2002; Kacperek 2001; Kobayashi 2000; Marcus 2001; RAD 1999; SFRADS 2002; Valmaggia 2002).

An update search done in March 2010 identified 487 reports of trials. After initial assessment by the Trials Search Co-ordinator, 477 references were excluded as they were deemed not relevant to the scope of the review and the review authors subsequently assessed ten reports. Of these ten reports, three were relevant trials (AMDLRTSG 2003; AMDRT 2004; Jaakkola 2005), six were ineligible trials and one was a report on quality of life outcomes in SFRADS 2002.

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Update searches run in May 2020 identified a further 1120 records (Figure 1). The Cochrane Information Specialist removed 217 duplicates and screened the remaining 903 reports, of which 804 were not relevant to the scope of the review. We reviewed the remaining 99 reports and discarded 80 records as not relevant. We obtained 19 full-text reports for potential inclusion in the review. We included 11 reports of four new studies - CABERNET 2013, INTREPID 2013, MERLOT 2016 and Osmanovic 2017 - and included a further three reports of the RAD 1999 study, which was already included in the previous version of this review. A newly published report from the MERLOT 2016 study giving results at 24 months was added to this review just prior to publication of this update.

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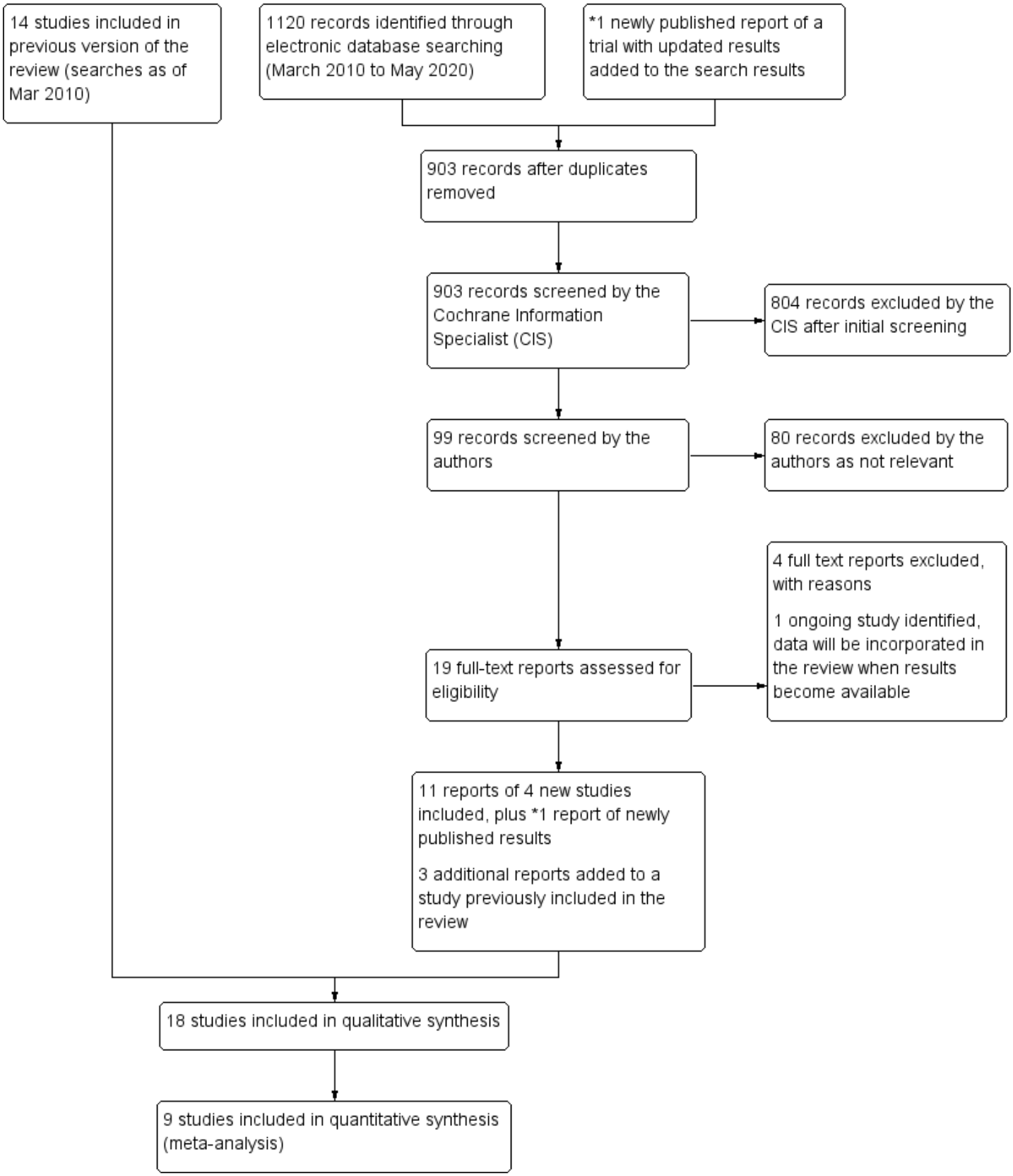
Figure 1. Study flow diagram.



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We excluded four studies. See Characteristics of excluded studies for details. We identified one ongoing study and will include it in the review when data becomes available (STAR (NCT02243878)).

Summary

The current edition of the review has 18 included studies (Characteristics of included studies), 22 excluded studies (Characteristics of excluded studies) and one ongoing study (Characteristics of ongoing studies).

Included studies

See Table 1 and Table 2.

Types of studies

All studies were parallel group randomised controlled trials; people were randomly allocated to treatment and one eye per person enrolled in the trial. In three trials it was not clear how many eyes were studied (Anders 1998; Ciulla 2002; Kacperek 2001). In Jaakkola 2005 two (out of 82) participants had both eyes enrolled.

Types of participants

The 18 trials randomised a total of 2430 people (2432 eyes). The studies took place in Germany (Anders 1998; Eter 2002; RAD 1999), the Netherlands (Bergink 1998), Finland (Jaakkola 2005), USA (AMDRT 2004; Char 1999; Ciulla 2002; Marcus 2001; Osmanovic 2017), Japan (AMDLRTSG 2003; Kobayashi 2000), UK (Kacperek 2001;MERLOT 2016; SFRADS 2002), and Switzerland (Valmaggia 2002). Three studies were multi-centre: CABERNET 2013 took place in US, Europe, Israel, South America, INTREPID 2013 took place in Europe and MERLOT 2016 was conducted in the UK.

The average age of participants in the studies ranged from 71 to 77 years (median average age 76 years). In most studies the majority of participants were women; the percentage female ranged from 30% to 69% (median 60%).

Most studies recruited participants with subfoveal CNV associated with AMD. INTREPID 2013 did not specify that the CNV had to be subfoveal. Most studies, with the exception of AMDLRTSG 2003, Anders 1998, INTREPID 2013 and Kacperek 2001, classified the CNV lesion as classic, occult or mixed (Table 2). The percentage of participants with classic CNV ranged between 12% (Marcus 2001;MERLOT 2016) and 57% (Valmaggia 2002). The percentage of participants with occult CNV ranged between 2% (SFRADS 2002) and 75% (MERLOT 2016).

Two studies did not specify visual acuity criteria for entry to the trial (Eter 2002; Valmaggia 2002). Most studies specified worst visual acuity in the study eye, in the region of 6/60 and 6/120 (AMDLRTSG 2003; AMDRT 2004; Anders 1998; Bergink 1998; Ciulla 2002; Jaakkola 2005; Kacperek 2001; Marcus 2001; RAD 1999; SFRADS 2002); two studies did not specify a worst acuity (Char 1999; Kobayashi 2000). More recent trials (CABERNET 2013; INTREPID 2013; MERLOT 2016; Osmanovic 2017) specified more moderate thresholds of visual impairment e.g. 6/12.

Types of intervention

Table 3 shows the detail of the radiation therapy and control in the different studies. Fifteen studies used external beam radiation therapy. The dosages ranged from 24 Gy (Bergink 1998; INTREPID 2013; Osmanovic 2017) to 7.5 Gy (Char 1999). Three studies used brachytherapy with a dose of 24 Gy (CABERNET 2013; MERLOT 2016) and 12.6 Gy delivered over 11 minutes (Jaakkola 2005).

Eleven of the studies gave no radiotherapy treatment to the control group (AMDLRTSG 2003; Anders 1998; Bergink 1998; CABERNET 2013; Char 1999; Eter 2002; Jaakkola 2005; Kacperek 2001; Kobayashi 2000; MERLOT 2016; SFRADS 2002); five studies used sham irradiation (Ciulla 2002; INTREPID 2013; Marcus 2001; Osmanovic 2017 ; RAD 1999) and one study used very low-dose irradiation (1 Gy) (Valmaggia 2002). In AMDRT 2004 some participants in the control group received sham irradiation and others received no treatment.

In the four more recent trials, radiation therapy was combined with anti-VEGF treatment - ranibizumab (CABERNET 2013; INTREPID 2013; MERLOT 2016) and either ranibizumab or bevacizumab (Osmanovic 2017).

Types of outcome measures

In most studies the primary outcome was visual acuity. This was usually 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 (AMDLRTSG 2003; AMDRT 2004; Kobayashi 2000; Osmanovic 2017; Valmaggia 2002) and appearance of the fundus on fluorescein angiography (Jaakkola 2005; Marcus 2001; RAD 1999). Near vision (SFRADS 2002) and reading ability (Valmaggia 2002) were also considered. Five studies specifically considered safety (AMDRT 2004; Kobayashi 2000; MERLOT 2016; Osmanovic 2017; SFRADS 2002). In INTREPID 2013 and MERLOT 2016 the primary outcome was the number of pro re nata (PRN) ranibizumab injections administered over 52 weeks.

Excluded studies

See 'Characteristics of excluded studies' table.

Risk of bias in included studies

Figure 2 and Figure 3 summarise the assessment of the risk of bias in included studies.

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Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

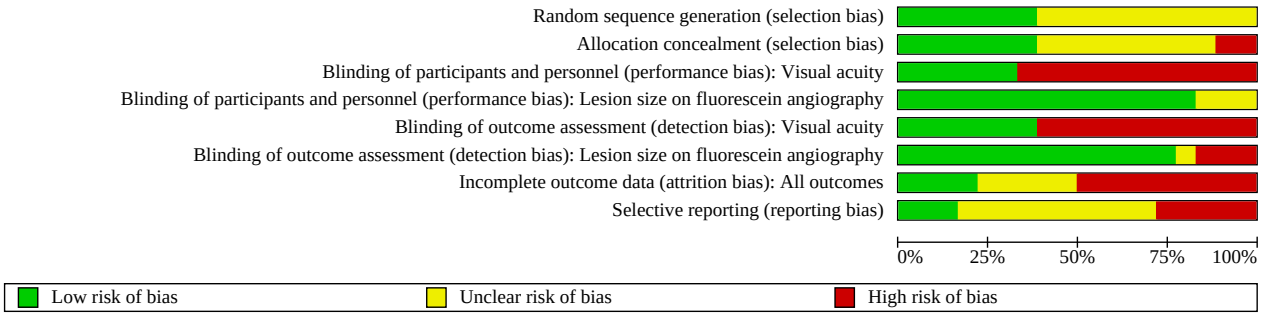

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Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

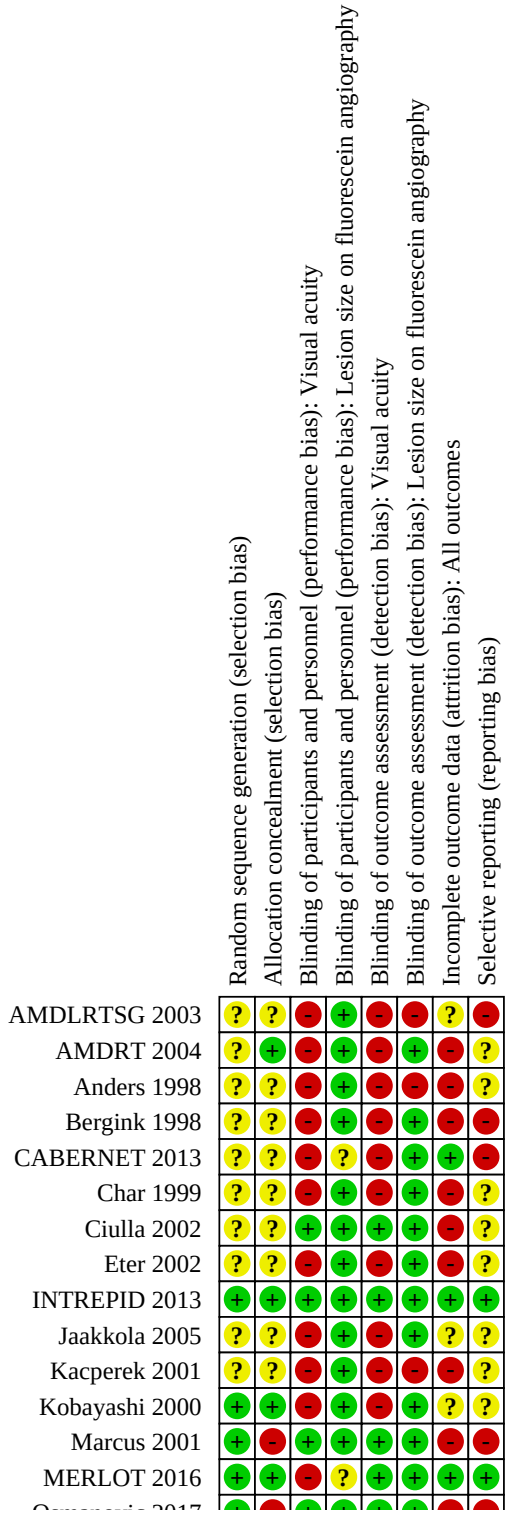

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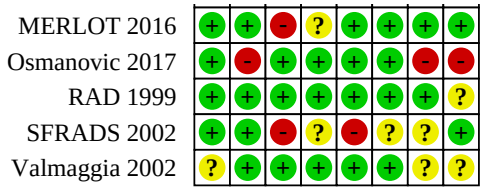
Figure 3. (Continued)



Allocation

For five studies, 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 (INTREPID 2013; Kobayashi 2000; MERLOT 2016; RAD 1999; SFRADS 2002).

In two studies the method of generating the allocation schedule was not clearly described but it was clear that the schedule was concealed (AMDRT 2004; Valmaggia 2002).

In one study the allocation was almost certainly unpredictable but it was printed out so clearly was not concealed (Marcus 2001). In another study the allocation was almost certainly unpredictable (coin toss) but was administered by an unmasked study co-ordinator and balanced in a way that was probably not random (Osmanovic 2017).

The other nine studies did not report the randomisation in sufficient detail (AMDLRTSG 2003; Anders 1998; Bergink 1998; CABERNET 2013; Char 1999; Ciulla 2002; Eter 2002; Jaakkola 2005; Kacperek 2001).

Blinding

We judged six studies to be at low risk of performance and detection bias for both visual acuity and lesion size (Ciulla 2002; INTREPID 2013; Marcus 2001; Osmanovic 2017; RAD 1999; Valmaggia 2002). All these studies gave convincing accounts of masking through sham radiotherapy and clear statements that participants, study personnel and outcome assessors were masked.

There were 12 studies that did not perform sham irradiation (AMDLRTSG 2003; AMDRT 2004; Anders 1998; Bergink 1998; CABERNET 2013; Char 1999; Eter 2002; Jaakkola 2005; Kacperek 2001; Kobayashi 2000; MERLOT 2016;SFRADS 2002). We judged all these studies at high risk of performance bias for visual acuity. We also judged them to be at high risk of detection bias for visual acuity with the exception of MERLOT 2016 where masked outcome assessors were used for visual acuity measurement.

We judged most studies to be at low risk of performance bias for lesion size on fluorescein angiography. We judged that masking, or lack of it, was unlikely to affect performance bias in studies where other treatments were not available. There were two studies where participants and personnel were unmasked and where the availability of anti-VEGF treatment meant that we were unsure as to the possibility of performance bias (CABERNET 2013; MERLOT 2016).

We felt that masking, or lack of masking, may well affect detection bias for lesion size on fluorescein angiography. Three studies did not report masking of assessment of lesion size and so were judged to be high risk of bias (AMDLRTSG 2003; Anders 1998; Kacperek 2001). The remaining studies were judged low risk of bias as the reports mentioned specific efforts to mask this outcome.

SFRADS 2002 did not report lesion size.

Incomplete outcome data

Only four studies were judged to be at low risk of attrition bias i.e. they reported high rates of follow-up that were reasonably equal between treatment groups (CABERNET 2013; INTREPID 2013; MERLOT 2016; RAD 1999). For five studies follow-up was not reported in enough detail to make a judgement (AMDLRTSG 2003; Jaakkola 2005; Kobayashi 2000; SFRADS 2002; Valmaggia 2002). The remaining studies were judged to be at high risk of attrition bias with lower proportions lost to follow-up and/or unequal follow-up between groups.

Selective reporting

In five studies not all the trials registry or protocol outcomes were reported (AMDLRTSG 2003; Bergink 1998; CABERNET 2013; Marcus 2001; Osmanovic 2017). In most of the other studies, in the absence of trials registry entries and protocols, it was unclear. In only two studies (INTREPID 2013; SFRADS 2002) there was a trials registry entry that also corresponded with the published reports.

Other potential sources of bias

No other potential sources of bias were noted.

Effects of interventions

See: **Summary of findings 1** Radiotherapy versus control for neovascular AMD; **Summary of findings 2** Radiotherapy combined with anti-VEGF versus anti-VEGF alone for neovascular AMD

See Summary of findings 1.

1. Radiotherapy versus control for neovascular AMD

Fourteen studies considered this comparison: 13 studies used external beam radiation therapy with doses ranging from 24 Gy (Bergink 1998) to 7.5 Gy (Char 1999) and one study used plaque brachytherapy with a dose of 12.6 Gy delivered over 11 minutes (Jaakkola 2005). Nine of the studies gave no radiotherapy treatment to the control group (AMDLRTSG 2003; Anders 1998; Bergink 1998; Char 1999; Eter 2002; Jaakkola 2005; Kacperek 2001; Kobayashi 2000; SFRADS 2002), three studies used sham irradiation (Ciulla 2002; Marcus 2001 ; RAD 1999), one study did a mixture of sham irradiation and observation (AMDRT 2004), and one study used very low-dose irradiation (1 Gy) (Valmaggia 2002).

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1.1 Loss of 3 or more lines of best-corrected visual acuity

Eight studies (811 eyes) reported data on this outcome at 12 months (Analysis 1.1). The results were heterogenous. Individual study estimates ranged from 0.42 (0.26 to 0.69) in favour of radiotherapy (Valmaggia 2002) to 1.22 (0.91 to 1.62) in favour of no radiotherapy (Marcus 2001). The I^2 value suggested that a substantial proportion of this variation was not due to chance (I^2 = 66%). The overall pooled value was 0.82 (95% CI 0.64 to 1.04). We judged this to be low-certainty evidence. We downgraded one level for risk of bias (6 of the 8 studies were high risk of bias in one or more domains) and downgraded one level for inconsistency (individual study effect estimates ranged from 0.42 to 1.22, I^2 = 66%). We did not downgrade an additional level for imprecision, even though the confidence intervals include 1 (no difference), because we had already downgraded for inconsistency which will have contributed to the imprecision of the pooled estimate.

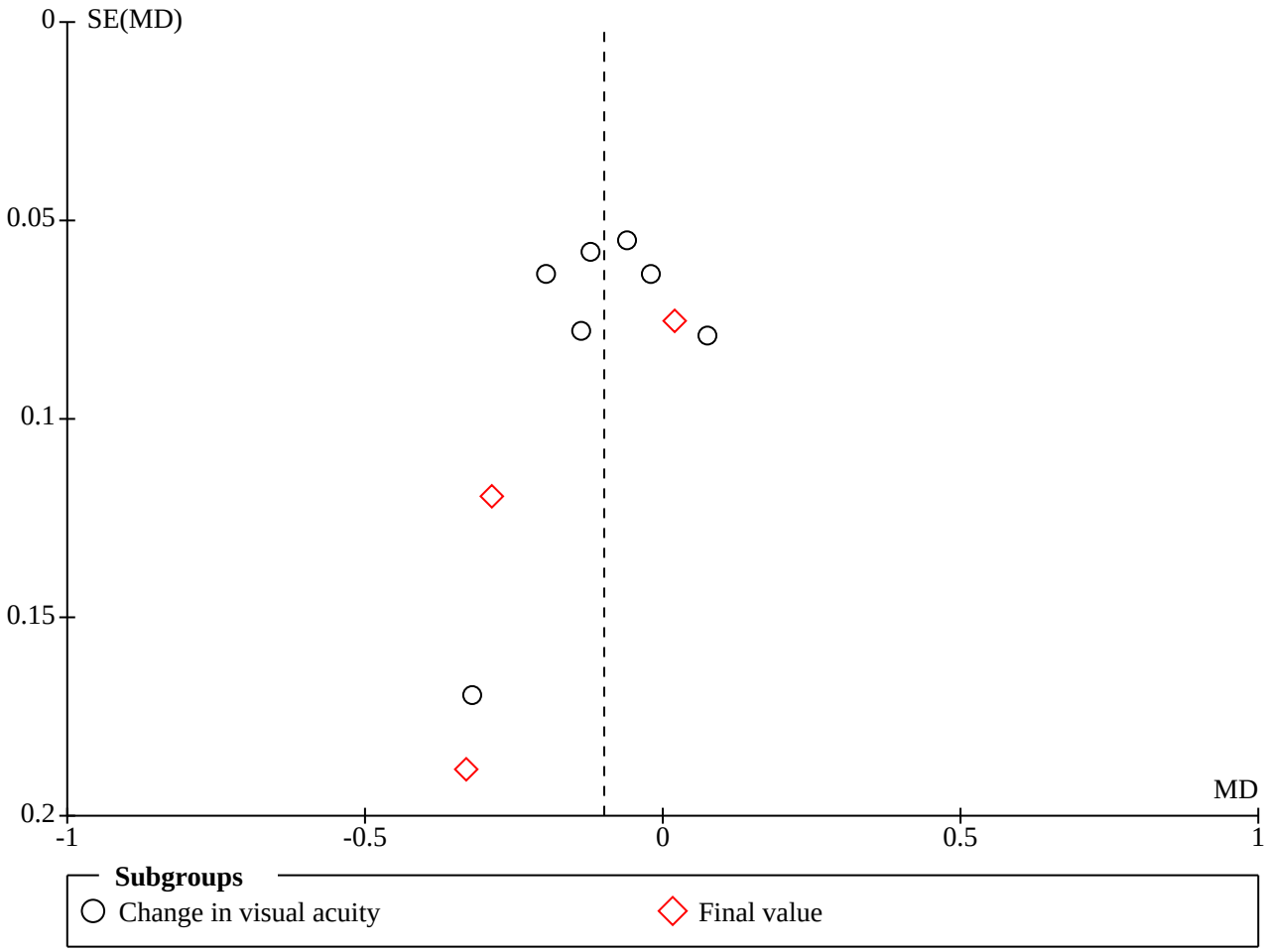
We performed subgroup analyses by dose of radiation, type of CNV and sham irradiation in the control group (Table 4). Although there were some differences between subgroups, none of the differences were statistically significant (test for interaction).

Five studies reported this outcome at 24 months (Analysis 1.2).there was heterogeneity with study results ranging from 0.58 (0.43 to 0.80) in favour of radiotherapy (Kobayashi 2000) to 1.03 (0.79 to 1.36) (Jaakkola 2005) (I^2 = 73%). The pooled risk ratio for studies of radiotherapy compared with no radiotherapy was 0.78 (95% CI 0.63 to 0.97).

1.2 Change in best-corrected visual acuity

Ten studies (883 eyes) reported mean change in best-corrected visual acuity or final best-corrected visual acuity at 12 months (Analysis 1.3). Study results ranged from -0.33 logMAR units in favour of radiotherapy (Ciulla 2002) to 0.07 logMAR units in favour of no radiotherapy (Marcus 2001) (I^2 = 49%). People receiving radiation therapy on average had a small (approximately 1 line) better visual acuity at 12 months (mean difference (MD) -0.10, 95% CI -0.17 to -0.03). These analyses may be at risk of selective outcome bias because continuous data may be ana lysed two ways - as final visual acuity or change in visual acuity from baseline. It is possible that the choice of which outcome to present was influenced by the results. We also noted an asymmetric funnel plot (Figure 4) possibly indicative of publication bias. We judged this to be low-certainty evidence, downgrading for risk of bias and publication bias.

Figure 4.



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We performed subgroup analyses by dose, type of CNV and sham irradiation in the control group (Table 5). Although there were some differences between subgroups, none of the differences were statistically significant (test for interaction).

1.3 Contrast sensitivity

Two studies reported contrast sensitivity measured on a Pelli-Robson chart (Jaakkola 2005; SFRADS 2002). There was a small difference in favour of radiation therapy at 12 months (MD 0.15 logunits, 95% CI 0.05 to 0.25; eyes = 267) (Analysis 1.5) and 24 months (MD 0.11 logunits, 95% CI 0.00 to 0.22; eyes = 257). We judged this to be low-certainty evidence downgrading one level for risk of bias (as neither of these two studies were masked) and one level for imprecision (confidence intervals close to 0).

Marcus 2001 reported the % contrast sensitivity threshold (Pelli-Robson chart). At 12 months there were some differences in the distribution in the treatment and observation groups but it was not possible to exclude the possibility that these were chance findings (P = 0.18).

Threshold %	Radiation (n = 37) n (%)	Control (n = 33) n (%)
≤ 10	8 (22)	15 (45)
11 to 49	10 (27)	5 (15)
≥ 50	19 (51)	13 (39)

1.4 New vessel growth

CNV was reported in different ways which makes it difficult to produce a summary estimate.

Size of CNV at 12 months (continuous)

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Study	Radiation therapy			Control			Mean difference (95% CI)	Comments
	Mean	SD	n	Mean	SD	n		
AMDLRTSG 2003	0.082	0.738	32	0.886	0.562	22	-0.80 (-1.15 to -0.46)	Disc diameters measured by fluorescein angiography. Follow-up: 12 months
Eter 2002	56	-	27	28	-	15	28.00 (-78.67 to 134.67) (estimated using reported P value of 0.61)	Average % increase in membrane size measured by fluorescein angiography. Follow-up: 6 months
Kobayashi 2000	8.305	9.967	45	8.172	7.674	39	0.13 (-3.65 to 3.91)	CNV area mm^2 measured using the Heidelberg Retina Tomograph Follow-up: 12 months
Marcus 2001	1.83	-	37	1.21	-	33	0.62 (-0.17 to 1.41) (estimated using reported P value of 0.13)	Increase in CNV (categories), measured using fluorescein angiograms and colour fundus photographs. Follow-up: 12 months

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SD: Standard deviation

Size of CNV at 12 months (dichotomous)

Study	Radiation therapy n/N	Control n/N	Risk ratio (95% CI)	Comments
Bergink 1998	7/34 (20%)	7/29 (25%)	0.81 (0.25 to 2.68)	Number of people in whom the size of the CNV doubled over 12 months measured using fluorescein angiography Follow-up: 12 months
Jaakkola 2005	33/43 (77%)	29/41 (71%)	1.37 (0.51 to 3.62)	CNV "less active" measured by fluorescein angiography Follow-up: 12 months

Results from other studies were as follows:

- Char 1999 reported no differences in CNV area and membrane edge but we were not able to extract data.
- Ciulla 2002 reported that the greatest linear dimension of CNV was not associated with treatment but data not reported.
- Valmaggia 2002 CNV size increased in all groups. The authors reported no significant differences between groups but data could not be extracted.

We judged this to be very low-certainty evidence. We downgraded one level for risk of bias (eight out of the nine studies reporting this outcome were high risk of bias in one or more domain); downgraded one level for imprecision (the individual studies were small with imprecise estimates); and downgraded one level for inconsistency (there was no consistent pattern to the individual study results).

1.5 Quality of life

Quality of life outcomes were reported in SFRADS 2002. Visual functioning was assessed by the Daily Living Tasks Dependent on Vision (DLTV) questionnaire (Hart 1999). There were no important differences between treatment and control groups on any dimension of the DLTV 12 or 24 months after treatment.

DLTV dimension	Change at 12 months mean (standard error)		Mean difference (95% CI)	Change at 24 months mean (standard error)		Mean difference (95% CI)
	Radiation therapy n = 87	Control n = 86		Radiation therapy n = 87	Control n = 88	
1	-10.6 (2.2)	-9.5 (2.6)	-1.10 (-7.77 to 5.57)	-13.5 (2.3)	-15.5 (3.3)	2.00 (-5.90 to 9.90)
2	-10.6 (2.2)	-7.8 (2.2)	-2.80 (-8.89 to 3.29)	-10.6 (2.5)	-11.9 (2.6)	1.30 (-5.77 to 8.37)
3	-8.4 (2.4)	-6.5 (2.3)	-1.90 (-8.41 to 4.61)	-8.2 (2.4)	-10.7 (1.7)	2.50 (-3.26 to 8.26)
4	-2.0 (3.1)	-3.2 (3.2)	1.20 (-7.53 to 9.93)	-3.2 (3.0)	-3.2 (2.4)	0.00 (-7.53 to 7.53)

We judged this to be low-certainty evidence. We downgraded one level for risk of bias study (study was not masked) and downgraded one level for imprecision (confidence intervals include 0).

1.6 Adverse outcomes

Reports of adverse outcomes are described in Table 6.

Six studies did not report on adverse effects (AMDLRTSG 2003; Char 1999; Ciulla 2002; Eter 2002; Jaakkola 2005; Kacperek 2001).

Eight studies (991 eyes) reported on adverse effects.

Radiation-associated retinopathy or neuropathy

Seven studies reported on radiation retinopathy, neuropathy or both. Five of these studies reported no radiation-associated adverse effects. One study of 88 eyes reported one case of possible radiation retinopathy. One study of 74 eyes graded retinal abnormalities in some detail and found that 72% of participants who had radiation compared with 71% of participants in the control group had retinal abnormalities resembling radiation retinopathy or choroidopathy.

- AMDRT 2004 (88 eyes): 1 case of possible radiation retinopathy

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- Bergink 1998 (74 eyes): 72% in radiation group, 71% in control group retinal abnormalities resembling radiation retinopathy or choroidopathy
- Kobayashi 2000 (101 eyes): reported no radiation-associated adverse effects
- Marcus 2001 (83 eyes): reported no radiation-associated adverse effects
- RAD 1999 (205 eyes): reported no radiation-associated adverse effects
- SFRADS 2002 (203 eyes): reported no radiation-associated adverse effects
- Valmaggia 2002 (161 eyes): reported no radiation-associated adverse effects

Cataract

Four studies reported cataract surgery or progression: events were generally low and no consistent evidence of any increased occurrence in the radiation group.

- AMDRT 2004 (88 eyes): cataract surgery on two participants, 1 in each group
- Kobayashi 2000 (101 eyes): cataract observed in 1 participant in radiation group
- Marcus 2001 (83 eyes): cataract progression similar in radiation and control groups
- RAD 1999 (295 eyes): cataract developed in 7 (10.3%) radiation group, 12 (16%) control group) (P = 0.218).

Dry eye

One study noted transient disturbance of the precorneal tear film but no evidence from the other 2 studies that reported dry eye of any increased risk with radiation therapy.

- AMDRT 2004 (88 eyes): 2 cases of ocular dryness in radiation group, 4 in control group
- RAD 1999 (205 eyes): dry eye symptoms in were recorded in 30 (40%) radiation group and 38 (45.2%) in control group (P = 0.525).
- SFRADS 2002 (203 eyes): transient disturbance of the precorneal tear film noted in treated participants

Other

- AMDRT 2004 (88 eyes): 5 deaths, 1 in radiation group and 4 in control group
- Anders 1998 (76 eyes): 3 subretinal haemorrhage in radiation group, 3 in control group
- Kobayashi 2000 (101 eyes): 2 people in radiation group complained of "transient conjunctival injection that resolved within 2 weeks"
- Marcus 2001 (83 eyes): 1 case of retinal detachment and 1 case of vitreous haemorrhage in the radiation group
- RAD 1999 (205 eyes): 4 deaths unrelated to radiation treatment, 3 in radiation group, 1 in control group

We judged this to be low-certainty evidence. We downgraded one level for risk of bias (eight out of the nine studies were high risk of bias in one or more domain) and downgraded one level for imprecision (the individual studies were small with imprecise estimates).

1.7 Number of anti-VEGF injections

This outcome was introduced in the current update and is only relevant to the next comparison where anti-VEGF was combined with radiotherapy.

2. Radiotherapy combined with anti-VEGF versus anti-VEGF alone for neovascular AMD

Four studies considered this comparison: two studies were of external beam radiotherapy (INTREPID 2013; Osmanovic 2017) and two studies of epimacular brachytherapy (CABERNET 2013; MERLOT 2016). INTREPID 2013 used IRay Radiotherapy System (Oraya Therapeutics, Newark, CA) to deliver ionising radiation targeted at the neovascular lesions. Two of the studies were three-arm studies with two intervention groups of 24 Gy and 16 Gy (INTREPID 2013; Osmanovic 2017). For the purposes of the analysis, we combined the intervention groups using the RevMan calculator. The other studies used 24 Gy dose. Three studies used ranibizumab (0.5 mg, PRN) in radiation and control groups; Osmanovic 2017 used either ranibizumab or bevacizumab. INTREPID 2013 and Osmanovic 2017 were sham-controlled.

2.1 Loss of 3 or more lines of best-corrected visual acuity

People receiving radiotherapy combined with anti-VEGF are probably more likely to lose 3 or more lines of BCVA over 12 months compared with people having anti-VEGF alone (RR 2.11, 95% CI 1.40 to 3.17; eyes = 1050; studies = 3; I^2 = 0%) (Analysis 2.1). Two of these studies were of epimacular brachytherapy (CABERNET 2013; MERLOT 2016) and these had a higher risk (RR 2.36 95% CI 1.49 to 3.74) than the one study of stereotactic radiotherapy (INTREPID 2013) (RR 1.24, 95% CI 0.50 to 3.11) although the formal test for subgroup differences was not statistically significant (P = 0.22). We judged this moderate-certainty evidence, downgrading for risk of bias (two of the studies were at risk of performance and detection bias).

Two studies reported data at 24 months (820 eyes) (CABERNET 2013; MERLOT 2016). There was an increased risk of loss of 3 or more lines in people treated with radiotherapy plus anti-VEGF compared with people treated with anti-VEGF alone (RR 2.39, 1.68 to 3.39) (Analysis 2.2).

2.2 Change in best-corrected visual acuity

Four studies reported this outcome at 12 months. Three of the studies reported logMAR letters. We converted this to logMAR score by multiplying the mean and standard deviation by 0.02 and changing the direction of the mean value by multiplying by -1 (as a larger logMAR score represents poorer vision). For two studies that had three arms we combined the 16 Gy and 24 Gy groups using the RevMan calculator. For Osmanovic 2017 standard deviations were not reported. We attempted to estimate the standard deviation using information in the paper (P values) but this produced values that appeared too small and gave this small study much too much weight in the analysis (of the order of 25%). We decided to impute the standard deviation by using values from the other included studies. The included studies ranged from standard deviations of approximately 0.2 to 0.3 so we chose a standard deviation of 0.25.

There was considerable heterogeneity (Analysis 2.4). Results ranged from a small mean difference of -0.03 logMAR in favour of radiotherapy combined with anti-VEGF (INTREPID 2013; Osmanovic 2017) to a mean difference of 0.13 logMAR (CABERNET 2013) and

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0.08 logMAR (MERLOT 2016) in favour of anti-VEGF alone. With an I^2 of 82% we took the decision not to pool these data. Subgroup analysis suggested a different effect in studies of external beam radiotherapy (MD -0.03 logMAR, 95% CI -0.09 to 0.03; participants = 252; studies = 2; I^2 = 0%) and studies of epimacular brachytherapy (MD 0.10 logMAR, 95% CI 0.05 to 0.15; participants = 820; studies = 2; I^2 = 50%, test for interaction P = 0.0007).

We judged this to be low-certainty evidence, downgrading for risk of bias (three of the four studies were high risk of bias in one or more domains) and inconsistency.

Two studies reported data at 24 months (819 eyes) (CABERNET 2013; MERLOT 2016). The mean difference in change visual acuity in the radiotherapy with anti-VEGF group was 0.17 logMAR (worse) (CI 0.11 to 0.23) compared with anti-VEGF alone (Analysis 2.2). Both studies were of epimacular brachytherapy.

2.3 Contrast sensitivity

None of the included studies reported this outcome.

2.4 New vessel growth

There were inconsistent results on size of the CNV at 12 months with one study finding increased lesion size with radiotherapy group whereas the other two studies found small differences (one in favour of radiotherapy, one not). One study did not report results disaggregated by treatment group. We judged this to be very low-certainty evidence, downgrading one level for risk of bias (two of the studies were at risk of performance and detection bias), one level for imprecision (two of the individual studies estimates were imprecise) and one level for inconsistency (there was no consistent pattern to the individual study results).

Size of CNV at 12 months (continuous)

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Study	Radiation therapy with anti-VEGF			Anti-VEGF alone			Mean difference (95% CI)	Comments
	Mean	SD	n	Mean	SD	n		
CABER-NET 2013	1.9	2.7	245	-3.0	7.2	124	4.90 (3.59 to 6.21)	Change in mean total lesion size in mm^2 at 24 months
INTRE-PID 2013	0.75	0.32	59	0.79	0.27	46	-0.04 (-0.15 to 0.07)	CNV area mm^2
MER-LOT 2016	1.2	8.3	219	0.4	7.6	110	0.80 (-1.00 to 2.60)	Change in total lesion size mm^2

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SD: Standard deviation

Osmanovic 2017 noted that the lesion area measured on FA decreased from 1.61 (SD 1.10) mm^2 at baseline to 0.73 (SD 0.85) mm^2 at one year for the overall study population. No differences were noted between the two intervention groups (16 and 24 Gy) and the sham irradiation group (data not reported for groups individually).

2.5 Quality of life

None of the included studies reported this outcome.

2.6 Adverse effects

In CABERNET 2013 the radiotherapy and anti-VEGF treatment group had a higher proportion of ocular adverse events (54%) compared to the anti-VEGF alone (18%). The majority of these adverse events were cataract. Overall 5% of the treatment group had radiation device-related adverse events (17 cases); 10 of these cases were radiation retinopathy.

INTREPID 2013 reported that adverse effects were similar across study arms and none were attributed to radiation.

In MERLOT 2016 the radiotherapy plus anti-VEGF group (n = 244) there were four cases of reduced visual acuity, one vitreous haemorrhage, three retinal haemorrhage, three retinal detachment, one vision blurred, one endophthalmitis, one vitreous floaters, two postoperative uveitis. In the anti-VEGF alone group (n = 119) there was one case of reduced visual acuity and one case of retinal haemorrhage.

Osmanovic 2017 reported no radiation associated adverse effects and no vascular adverse events. Four out of 13 phakic eyes had cataract progression (one from the control and three from the radiation group).

2.7 Number of anti-VEGF injections

This outcome was introduced in the current update and is only relevant to the four studies that combined anti-VEGF with radiotherapy (CABERNET 2013; INTREPID 2013; MERLOT 2016; Osmanovic 2017).

There were some differences in average number of injections given between the four studies. In three of the four studies, the anti-VEGF alone group on average received more injections.

	Radiotherapy with anti-VEGF		**Anti-VEGF alone**	
Study	**Number of loading injections planned**	**Total mean number of injections (SD)**	**Number of loading injections planned**	**Total mean number of injections (SD)**
CABERNET 2013	2 (baseline, month 1)	12 months: (3.7) 24 months: (h6.2)	3 (baseline, month 1, month 2)	12 months: (6.2) 24 months: (10.4)
INTREPID 2013	1 (baseline)	12 months: 16-Gy: 2.64 (2.46) (median, 2; range, 0 to 10) 24-Gy: 2.43 (2.40) (median, 2; range, 0 to 10)	1 (baseline)	12 months: 3.74 (2.57) (median, 3.5; range, 0 to 10)
MERLOT 2016	0*	4.8 (3.2) 4.5 (3.8)	0*	4.1 (2.4) 4.2 (2.7)
Osmanovic 2017	3	16-Gy: 3.52 (range 4 to 8) 24-Gy: 3.83 (range 3 to 5)	3	6.13 (range 3 to 8)

SD: Standard deviation

*Quote: "Inclusion criteria included completion of a loading phase of 3 anti-VEGF induction injections, followed by ongoing monthly PRN therapy, with a minimum of 4 ranibizumab treatments in the previous 12 months or 2 ranibizumab treatments in the previous 6 months."

DISCUSSION

Summary of main results

We included 18 studies (n = 2430 people, 2432 eyes) of radiation therapy with dosages ranging from 7.5 to 24 Gy.These studies mainly took place in Europe and North America but two studies were from Japan and one multicentre study included sites in South America. Three of these studies investigated brachytherapy (plaque and epimacular), the rest were studies of external beam radiotherapy including one trial of stereotactic radiotherapy. Four studies compared radiotherapy combined with anti-vascular

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endothelial growth factor (anti-VEGF) with anti-VEGF alone. Eleven of the studies gave no radiotherapy treatment to the control group; five studies used sham irradiation; and one study used very low-dose irradiation (1 Gy) and one study used a mixture of sham irradiation and no treatment. Fifteen studies were judged to be at high risk of bias in one or more domains.

For the comparison radiotherapy versus no radiotherapy, our results suggest little or no difference in loss of 3 lines of vision at 12 months (low-certainty evidence). We observed a small benefit in average visual acuity at 12 months for radiotherapy; there was some evidence of possible publication bias (low-certainty evidence). Low-certainty evidence suggested a small benefit in average contrast sensitivity at 12 months but the effect was small and we judged the certainty of the evidence to be low. Growth of new vessels (largely change in CNV size) was variably reported and It was not possible to produce a summary estimate of this outcome. The studies were small with imprecise estimates and there was no consistent pattern to the study results (very low-certainty evidence). Quality of life was only reported in one study of 199 people; there was no clear differences between treatment and control groups (low-certainty evidence). Six out of 14 studies did not report on adverse effects. Seven studies reported on radiation retinopathy or neuropathy or both. Five of these studies reported no radiation-associated adverse effects. One study of 88 eyes reported one case of possible radiation retinopathy. One study of 74 eyes graded retinal abnormalities in some detail and found that 72% of participants who had radiation, compared with 71% of participants in the control group, had retinal abnormalities resembling radiation retinopathy or choroidopathy. Four studies reported cataract surgery or progression: events were generally low and no consistent evidence of any increased occurrence in the radiation group. One study noted transient disturbance of the precorneal tear film but no evidence from the other two studies that reported dry eye of any increased risk with radiation therapy. None of the participants received anti-VEGF injections.

When radiotherapy was combined with anti-VEGF and compared to anti-VEGF alone, *p*eople receiving radiotherapy plus anti-VEGF were had worse visual outcomes which was probably largely attributable to the epimacular brachytherapy technique which involves pars plana vitrectomy. Anti-VEGF regimens with fewer injections may be associated with less visual gain (Kim 2016, Li 2020) and this may be another explanation for worse visual outcomes in the radiotherapy group in unmasked studies. None of the included studies reported contrast sensitivity or quality of life. Growth of new vessels (largely change in CNV size) was variably reported in three studies (803 eyes); It was not possible to produce a summary estimate. There was no consistent pattern to the study results (very low-certainty evidence). For adverse outcomes, variable results were reported in the 4 studies. In 3 studies reports of adverse events were low and no radiation-associated adverse events reported. In one study the radiotherapy and anti-VEGF treatment group had a higher proportion of ocular adverse events (54%) compared to the anti-VEGF alone (18%). The majority of these adverse events were cataract. Overall 5% of the treatment group had radiation device-related adverse events (17 cases); 10 of these cases were radiation retinopathy.

There is one large ongoing study (STAR (NCT02243878)) involving over 400 participants in 10 UK centres. Stereotactic radiotherapy combined with ranibizumab is being compared to sham radiotherapy plus ranibizumab alone with estimated study completion in 2024.

Overall completeness and applicability of evidence

Although there are 18 trials published, the overall completeness of the evidence is less than might be expected from the number of trials. This is because of the different dosages used, different outcome measures and different follow-up times reported. Most studies included in this review took place before the use of anti-VEGF became widespread, and before the development of modern radiotherapy techniques, such as stereotactic radiotherapy. We observed worse visual outcomes with epimacular brachytherapy, and there is an increased risk of adverse events with that technique. The role of modern radiotherapy, in combination with anti-VEGF, is currently uncertain. It may offer the potential to reduce the need for anti-VEGF retreatment, and there are ongoing studies addressing this question.

Quality of the evidence

The evidence was largely judged to be of low-certainty, depending on the outcome. We downgraded for risk of bias because of limitations in the studies, particularly in regard to selection, performance and detection bias. We also downgraded for imprecision because the confidence intervals included no effect or clinically unimportant differences. We could assess publication bias for only one outcome - change in visual acuity at 12 months - and this showed an asymmetric plot indicative of publication bias.

The applicability of this evidence is also limited by differences in inclusion criteria and study design among studies. For example, in CABERNET 2013, an unmasked study, patients received a loading phase of three injections in the anti-VEGF-alone arm and two injections in the combined radiotherapy arm. The lack of masking may have led to a further tendency to prescribe fewer injections in the combination arm, which may have led to less visual gain. Lack of masking may have influenced the attitude towards prescription of anti-VEGF injections also in Osmanovic 2017. Another limitation is in the inclusion of patients with newly diagnosed versus chronic active CNV, such as in Osmanovic 2017 and INTREPID 2013. Finally, the mean number of injections was small in some studies. This caused skewed estimates, with mean values being similar to their standard deviations.

Potential biases in the review process

There have been many changes to both AMD treatment and Cochrane methods since the protocol for this review was first published in 2002. As such, many of the decisions have been made post-hoc. In the case of Cochrane methods, the introduction of new methods is unlikely to have introduced bias, indeed, it is likely to have improved the overall robustness of the review. When it comes to incorporating new evidence, the key decision was how to incorporate trials where radiotherapy was combined with anti-VEGF. Given that the baseline risk for many outcomes included in this review is so different with anti-VEGF, and given the overall context in which the studies took place, we took the decision to add in a separate comparison to this review. An alternative approach may have been to consider these as a subgroup. However, given that the effects were so different, and that we included an additional outcome of number of injections, we felt that it was clearer to consider these as a separate comparison. We feel that either approach would have produced similar results. Similarly,

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we had discussion about the heterogeneity in radiotherapy interventions in the more recent studies. We considered external beam radiotherapy and epimacular brachytherapy as subgroups; as the results were quite different we have presented the results of this subgroup analysis in the abstract.

Agreements and disagreements with other studies or reviews

Other reviews, in general, acknowledge the disappointing results with external beam radiotherapy and focus on the potential role of more targeted radiotherapy techniques - either stereotactic and brachytherapy (plaque or epimacular) - in combination with anti-VEGF therapy (Englander 2013; Kishan 2013; Mendez 2013; Silva 2011). These other reviews are narrative, rather than systematic, and discuss a broader section of the literature, including non-randomised studies.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review are uncertain regarding the use of radiotherapy in people with neovascular AMD; the majority of the studies took place before the use of anti-VEGF became widespread and before the development of modern radiotherapy techniques such as stereotactic radiotherapy. Visual outcomes with epimacular brachytherapy are likely to be worse and there is an increased risk of adverse events with that technique. The role of modern radiotherapy, in combination with anti-VEGF, is currently uncertain; ongoing studies are assessing its role in reducing the need for anti-VEGF retreatment.

Implications for research

Given the results of this review, further research on radiotherapy for neovascular AMD may not be justified until current ongoing studies, in particular the STAR trial, have reported. 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. Current ongoing studies are addressing the issue as to whether radiotherapy combined with anti-VEGF may reduce the need to anti-VEGF retreatment.

ACKNOWLEDGEMENTS

The Cochrane Eyes and Vision (CEV) editorial team prepared and executed the electronic searches. We are grateful to Rebecca Wong, Catey Bunce and Roberta Scherer for peer review. We thank Zoe Ockrim and Vasuki Sivagnanavel for their contributions to previous versions of this review. We thanks Anupa Shah, Managing Editor for CEV for her assistance throughout the review process. We would also like to thank Takehiro Yamashita and Ryo Asaoka for translating a Japanese article for the 2010 update.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

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AMDLRTSG 2003

Study characteristics	
Methods	Parallel group RCT One eye per person, unclear how selected
Participants	Country: Japan Number of participants (eyes) enrolled: NR Number of participants (eyes) excluded after randomisation: NR Number of participants (eyes) ana lysed at 12 months: 69 (69) Average age: 72 years (range NR) Sex: 30% women Inclusion criteria: • At least 60 years of age • Worsening of symptoms or clinical features within 12 months • A best corrected visual acuity is 20/200 or more • CNV with AMD was assessed by FA or IA • A maximum CNV size was one optic-disk diameter • CNV located at the fovea or the edge of CNV within 200 micro meters from the fovea • Signature on the Informed Consent Form with ability to fully understand the informed consent7 Exclusion criteria: • Under 60 years of age • Difficult to asses the size of CNV • Cataract with less-visible fundus • History of diabetes • History of hypertension • Optic neuropathy
Interventions	Intervention: (n=38) • External beam radiation therapy (10 fractions of 2Gy) • Duration: NR Comparator: (n=31) • Observation
Outcomes	Primary: NR Secondary: NR Reported: • Visual acuity (logMAR) • Size of CNV (by FA or IA). Follow-up: 12 months
Notes	Date conducted: NR Sources of funding: NR

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AMDLRTSG 2003 *(Continued)*

	Declaration of interest: NR
	Trial id: NR
	Information from translation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: not reported
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not reported
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Judgement comment: masking was not mentioned in the report. We judged that participants and personnel were probably not masked which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Judgement comment: masking was not mentioned in the report. We judged that participants and personnel were probably not masked but felt that lack of masking was unlikely to lead to performance bias for this outcome.
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Judgement comment: masking was not mentioned in the report. It is possible that an individual's performance on the visual acuity test could be influenced by their perceptions as to which treatment they received.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	High risk	Judgement comment: masking was not mentioned in the report.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	Study was planned as 2-year study enrolling 100 participants but only 69 participants reported after one year.

AMDRT 2004

Study characteristics

Methods	Parallel group RCT
	One eye per person
	Multicentre study: 10 sites
Participants	Country: US
	Number of participants (eyes) randomised: 88 (88)
	Number of participants (eyes) excluded after randomisation: NR

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AMDRT 2004 *(Continued)*

	Number of participants (eyes) ana lysed at 12 months: 62 (62) Average age: 77 years (63 to 92) Sex: 58% women Inclusion criteria: • Age 50 or older • New or recurrent CNV secondary to AMD • Occult CNV or minimally classic or predominately classic subfoveal CNV • CNV not amenable to laser treatment or participant refuses • <50% fibrosis • No ocular histoplasmosis • No ocular conditions precluding good photography • No other ocular condition likely to affect visual acuity in 2 years • Myopia <=8 diopters • Acuity >= 20/320 Exclusion criteria: • Diabetes • Prior ocular/periocular radiation • CNV secondary to non-AMD causes • Prior or current chemotherapy • History of macula affecting drugs
Interventions	Intervention: (n=41) • External beam radiation therapy (5 fractions of 4 Gy) Comparator: (n=47) • Observation (n=25) • Sham radiotherapy (n=22)
Outcomes	Primary: • Loss of 3 or more lines of visual acuity • 5 to 8 working days Secondary: • Lesion size graded on fluorescein angiography. • Side effects. Follow-up: 12 months
Notes	Full trial name: Age-related macular degeneration radiotherapy trial (AMDRT). Date conducted: January 2000 to December 2001 Sources of funding: Supported by grant R21 EY12341 from the National Eye Institute, National Institutes of Health, Department of Health and Human Services and institutional funds from each of the participating centres. Declaration of interest: NR Trial id: NR Planned sample size 100 participants; stopped early because of a low rate of recruitment.

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AMDRT 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "Randomised treatment assignment schedules, stratified by lesion type (new or recurrent) and status of blood (<50% or >=50% of the lesion) were generated for each clinical site" Page 819, methods, enrolment and randomisation procedures, 2nd paragraph. Judgement comment: not clear how the allocation schedule was generated.
Allocation concealment (selection bias)	Low risk	Quote "After required examinations and photography were completed, an eligibility checklist was faxed to the Coordinating Center. The enrolling ophthalmologist and clinic coordinator verbally confirmed eligibility of the patient by telephone with a Coordinating Center staff member. For centres performing sham radiotherapy, sealed, black-lined security envelopes containing a randomized assignment were provided to the ophthalmology clinical staff. At enrollment, the clinic co-ordinator confirmed with the Co-ordinating center the assignment of the patient to the next sequentially numbered envelope for the appropriate strata. The sealed envelope was sent to the Radiation Oncology Department and opened by the radiation oncologist and radiation physicist immediately before treatment. For centers not performing sham radiotherapy, the coordinator called the Co-ordinating center to obtain the treatment assignment" Page 819, methods, enrolment and randomisation procedures, 1st and 2nd paragraphs.
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Quote: "At the outset, each center had the option to choose sham radiotherapy or observation only as the control treatment for active radiotherapy. Three centers chose sham radiotherapy." Page 819, methods, 1st paragraph. Judgement comment: participants and personnel were not masked in 7 out of 10 centres (25/47 participants) which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Quote: "At the outset, each center had the option to choose sham radiotherapy or observation only as the control treatment for active radiotherapy. Three centers chose sham radiotherapy." Page 819, methods, 1st paragraph. Judgement comment: participants and personnel were not masked in 7 out of 10 centres (25/47 participants) . We felt that lack of masking was unlikely to lead to performance bias for this outcome.
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Quote: "At the outset, each center had the option to choose sham radiotherapy or observation only as the control treatment for active radiotherapy. Three centers chose sham radiotherapy." Page 819, methods, 1st paragraph. "During follow-up, examiners were masked to the patient's treatment assignment" Page 820, 1st paragraph. Judgement comment: it was obvious which group received radiotherapy. Only 3 out of 10 centres chose to perform sham radiotherapy. Only some of the control group (22/47) received sham radiotherapy. Visual acuity assessment was masked to treatment group, however, it is possible that an individual's performance on the visual acuity test could be influenced by their perceptions as to which treatment they received.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Certified photographers performed all fundus photography and fluorescein angiography following SST protocols. Initial visit photography was

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AMDRT 2004 *(Continued)*

Lesion size on fluorescein angiography		required within 42 days of enrollment. Expert readers at the FPRC, masked to treatment assignment, reviewed all baseline photographs and angiograms for eligibility." Page 820, photography and fluorescein angiography, 1st and 2nd paragraphs. Although the report does not explicitly state that photograph graders were masked to treatment assignment when considering follow-up photographs and angiograms it is highly likely that they were and it is unlikely that a participant's knowledge of treatment group would influence the appearance of photographs or fluorescein angiograms.
Incomplete outcome data (attrition bias) All outcomes	High risk	31/41 (76%) in treatment group seen at 12 months; 31/47 (66%) of the control group seen at 12 months. 12 randomised participants were subsequently considered ineligible; all these participants included in the analysis. 5 participants did not get the treatment they were assigned but were analysed in the original group to which they were assigned. Quote: "Among all missed visits, the most common reason for not completing the visit was patient refusal; other reasons were illness and transportation problems" The follow-up in the control group was rather low which is why this is marked "no".
Selective reporting (reporting bias)	Unclear risk	No access to study protocol or trial registry entry.

Anders 1998

Study characteristics	
Methods	Parallel group RCT Unclear whether one or both eyes enrolled
Participants	Country: Germany Number of participants (eyes) randomised: 76 (?) Number of participants (eyes) excluded after randomisation:NR Number of participants (eyes) analysed: 76 (6 months) and 37 (12 months) Average age: 77 years (range NR) Sex: 67% women Inclusion criteria: • fluorescein angiography detectable classic subfoveal choroidal neovascular membranes; • no foveal bleeding • history of severe visual impairment does not exceed 6 months • visual acuity is not better than 0.5 and no worse than 0.05 • age over 50 years • no previous laser photocoagulation of macular • no previous irradiation of the region • no other eye diseases that could deteriorate the visual acuity • opportunity to participate in further follow-up up to 5 years

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Anders 1998 *(Continued)*

	Exclusion criteria: NR
Interventions	Intervention: (n=39) • External beam radiation therapy (6 fractions of 2Gy) • Duration: 8 days Comparator: (n=37) • Observation
Outcomes	Primary: NR Secondary: NR Reported: • Near visual acuity • Distance visual acuity • Metamorphopsia by Amslernetz • Complications including subretinal haemorrhage and lens opacity Follow-up: 3, 6 and 12 months
Notes	Date conducted:NR Sources of funding: NR Declaration of interest: NR Trial id: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: not reported.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not reported.
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Judgement comment: masking was not mentioned in the report. We judged that participants and personnel were probably not masked which may have affected visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Judgement comment: masking was not mentioned in the report. We judged that participants and personnel were probably not masked but felt that lack of masking was unlikely to lead to performance bias for this outcome.
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Not reported and groups different
Blinding of outcome assessment (detection bias)	High risk	Not reported and groups different

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Anders 1998 *(Continued)*

Lesion size on fluorescein angiography		
Incomplete outcome data (attrition bias) All outcomes	High risk	19/39 (49%) radiation group and 18/37 (49%) control group seen at 12 months. No information as to the reason for loss to follow-up given.
Selective reporting (reporting bias)	Unclear risk	No access to study protocol or trial registry entry.

Bergink 1998

Study characteristics	
Methods	Parallel group RCT One eye per person, unclear how eye was selected - described as "affected eye"
Participants	Country: The Netherlands Number of participants (eyes) randomised: 74 (74) Number of participants (eyes) excluded after randomisation: 3 (3) Number of participants (eyes) analysed: 68 (68) (at 3 months) 63 (63) (at 12 months) Average age: 75 years (range NR) Sex: 56% women. Inclusion criteria: • Recent drop in central vision (within 2 months) • Best-corrected Snellen visual acuity >0.1 • Angiographically proven classic, occult or mixed type subfoveal CNV • Clinical signs of ARM, e.g., drusen or pigment epithelial changes • Age ≥ 55 years • Informed consent • No previous laser photocoagulation in the macular area • No radiation treatment for ear, nose, throat or brain disease • No diabetes mellitus Exclusion criteria: NR
Interventions	Intervention: (n=36)* • External beam radiation therapy (4 fractions of 6Gy) • Duration: 3 weeks Comparator: (n=32)* • Observation *Number randomised not reported. This is the number in each group at 3 months.
Outcomes	Primary: NR but sample size calculation based on loss of 1 or more lines of Snellen acuity ending up with visual acuity <0.1. Secondary: NR

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Bergink 1998 *(Continued)*

	Reported: • Visual acuity (loss of 3 or more lines and loss of 6 or more lines) • Size of the CNV Follow-up: 3, 6 and 12 months
Notes	Date conducted: NR Sources of funding:NR Declaration of interest: NR Trial id: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...patients were assigned randomly to either radiation treatment or observation." Page 322 Judgement comment: not clear how the allocation schedule was generated.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not reported.
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Quote: "The patients in the control group did not receive a sham radiation treatment" Page 322. Judgement comment: participants and personnel were not masked which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Quote: "The patients in the control group did not receive a sham radiation treatment" Page 322. Judgement comment: participants and personnel were not masked but we felt that lack of masking was unlikely to lead to performance bias for this outcome.
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Quote: "The patients in the control group did not receive a sham radiation treatment" Page 322.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "The readers were blinded for treatment status." Page 322
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote "Initially, 74 patients were included in the study. Of these, one died and two stopped before the first control, one because of fear of malignancies due to the treatment. In addition, one was excluded because of previously unnoted diabetes mellitus and two patients showed insufficient evidence for CNV on the angiogram later on. As a result, 68 patients, 36 in the treatment group and 32 in the observation group completed at least 3 months/ follow-up. Twelve months follow-up was obtained in 63 patients." Page 322. No information on the numbers originally randomised to treatment and control.

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Bergink 1998 *(Continued)*

Selective reporting (reporting bias)	High risk	Outcome on which sample size was based not reported

CABERNET 2013

Study characteristics	
Methods	Parallel group RCT One eye included in study; if both eyes were eligible, then the eye with the worse VA was treated.
Participants	Country: US, Europe, Israel, South America Number of participants (eyes) randomised: 494 (494) Number of participants (eyes) excluded after randomisation: 0 Number of participants (eyes) analysed: 457 (457) Average age: 77 years (range 50 to 96) Sex: 68% women Inclusion criteria: • age 50 or older • predominantly classic, minimally classic, or occult with no classic lesions, as determined by the Investigator, secondary to AMD, with a total lesion size (including blood, scarring, and neovascularization) of ≤ 12 total disc areas (21.24 mm^2), and a GLD ≤5.4 mm • primary (newly diagnosed and untreated) or recurrent lesions (previously diagnosed and regressed but currently presenting with a new, active component) • ETDRS best corrected visual acuity of 69 to 24 letters (20/40 to 20/320 Snellen Equivalent) in the study eye • if both eyes eligible, one with worse acuity selected; if only one eye eligible, vision in the non-study eye was 20/400 or better • subretinal haemorrhage (if any) not more than 50% of total lesion size, and not involving the subfoveal space • minimally classic and occult with no classic lesions must have evidence of presumed recent disease progression defined as:(i) The presence of subretinal haemorrhage and/or fluid and/or lipid or (ii) loss of one or more lines of vision (ETDRS or equivalent) during previous six months or FA documented lesion growth by ≥ 10% during past 6 months • women post-menopausal #1 year or surgically sterilized or negative serum pregnancy test required within 14 days prior to randomisation Exclusion criteria: In the study eye: • prior or concurrent treatment for neovascular AMD or glaucoma • prior or concomitant disease • CNV lesion contained more than 25% scarring and/or atrophy • inadequate pupillary dilation or significant media opacities • vitreous haemorrhage • history of rhegmatogenous retinal detachment or macular hole • any intraocular surgery of the study eye within 12 weeks prior to the screening visit, with the exception of cataract surgery

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CABERNET 2013 *(Continued)*

	• Other systemic conditions/treatments and/or any other condition preventing from completing the study (details in online appendices to published paper)
Interventions	Intervention: (n=331) • Epimacular brachytherapy (standardised point dose of 24Gy) • 2 intravitreal injections of 0.5mg ranibizumab, one at the end of surgery and one 30 days later Comparator: (n=163) • Ranibizumab (0.5mg) 3 injections, over 3 months followed by quarterly injections Epimacular brachytherapy was delivered by an intraocular strontium 90/yttrium 90 (Sr^{90}/Y^{90}) applicator device designed to deliver local, targeted radiation to the neovascular tissue associated with wet AMD. Participants were followed up monthly and received an additional injection if one or more of the retreatment criteria were met. Retreatment was mandated if any of the following applied: loss of 10 letters of VA, verified by repeat testing within 7 days; 50-µm increase in OCT central retinal thickness; new subretinal haemorrhage;or new neovascularization visible using FA.
Outcomes	Primary (at 24 months) • Proportion of participants losing fewer than 15 ETDRS letters of BCVA from baseline • Proportion of participants gaining 15 ETDRS letters or more of BCVA Secondary (at 24 months) • Mean change in BCVA • Mean change in FA lesion size • Mean change in OCT central foveal thickness • Mean number of ranibizumab retreatments Follow-up:12 and 24 months
Notes	Full study name: CNV Secondary to AMD Treated with BEta RadiatioN Epiretinal Therapy (CABERNET) Date conducted: June 2007 to September 2009 Sources of funding: Study was sponsored by the manufacturer of the device - NeoVista Declaration of interest: *"The sponsor (NeoVista, Inc) participated in the design, conduct, data collection, data management, data analysis, interpretation of the data, preparation, review, and approval of the manuscript"* Trial registration ID number: NCT00454389

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was stratified by study center, type of lesion (predominantly classic, minimally classic, or occult), and baseline VA (53 letters or 53 letters) using a 2:1 randomization scheme in favor of EMBT" Page 319 Judgement comment: unclear how the schedule was generated.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not reported

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CABERNET 2013 *(Continued)*

Blinding of participants and personnel (performance bias) Visual acuity	High risk	Quote: "Because this study involved a surgical intervention and sham surgery with a nonradioactive probe was not believed to be ethically appropriate, masking to study treatment was not possible for the treating surgeon and the patient; however, the VA examiner and the reading centers that reviewed all optical coherence tomography (OCT) and FA images were masked." Page 319 Judgement comment: participants and personnel were not masked which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Unclear risk	Quote: "Because this study involved a surgical intervention and sham surgery with a nonradioactive probe was not believed to be ethically appropriate, masking to study treatment was not possible for the treating surgeon and the patient; however, the VA examiner and the reading centers that reviewed all optical coherence tomography (OCT) and FA images were masked." Page 319 Judgement comment: participants and personnel were not masked. We felt that it was unclear what effect this would have on lesion progression.
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Quote: "Because this study involved a surgical intervention and sham surgery with a nonradioactive probe was not believed to be ethically appropriate, masking to study treatment was not possible for the treating surgeon and the patient; however, the VA examiner and the reading centers that reviewed all optical coherence tomography (OCT) and FA images were masked." Page 319 Although visual acuity assessment was masked to treatment group, physicians and participants were not. It is possible that an individual's performance on the visual acuity test could be influenced by their perceptions as to which treatment they received.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "Because this study involved a surgical intervention and sham surgery with a nonradioactive probe was not believed to be ethically appropriate, masking to study treatment was not possible for the treating surgeon and the patient; however, the VA examiner and the reading centers that reviewed all optical coherence tomography (OCT) and FA images were masked." Page 319
Incomplete outcome data (attrition bias) All outcomes	Low risk	302/331 (91%) in the intervention arm were analysed and 155/163 (95%) of comparator arm.
Selective reporting (reporting bias)	High risk	Outcomes pre-specified at 12 months (on trials registry entry) but reported at 24 months.

Char 1999

Study characteristics	
Methods	Parallel group RCT One eye per person. *"In patients with bilateral disease, all had marked disparity in visual acuity between the two eyes. The eye with better vision, having worse than 20/40 best-corrected visual acuity, was entered in the trial, except for five patients in whom the treated eye was worse than 20/40 and the fellow eye had better acuity."*
Participants	Country: USA. Number of participants (eyes) randomised: 27 (27) Number of participants (eyes) excluded after randomisation: NR

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Char 1999 *(Continued)*

	Number of participants (eyes) analysed: 27 (27) Average age: 76 years (range 64 to 89) Sex: 52% women Inclusion criteria: • Subfoveal CNV secondary to AMD with visual acuity less than 20/40. Exclusion criteria: NR
Interventions	Intervention: (n=14) • External beam radiation therapy (1 fraction of 7.5 Gy) Comparator: (n=13) • Observation
Outcomes	Primary: NR Secondary: NR Reported: • Visual acuity (ETDRS chart) • Changes in subretinal neovascular area and membrane edge Follow-up: Every 3 months, average follow-up 17 months (range 0 to 32 months)
Notes	Date conducted: NR Sources of funding: *"This study was supported in part by a grant from That Man May See, San Francisco, California, an unrestricted grant from Research to Prevent Blindness Inc, New York, New York, and an unrestricted grant from the Tumori Foundation, San Francisco, California."* Declaration of interest: NR Trial id: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to either no treatment or to treatment with...." Page 575, methods. Judgement comment: unclear how the allocation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not reported.
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Quote: "... visual acuity examination with refraction by a trained ophthalmic technician, who was masked to the patients' status in the trial" Page 575, methods. Judgement comment: participants and personnel were not masked which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Quote: "Initial and serial fluorescein angiograms were read in a masked manner by two observers...." Page 575, methods.

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Char 1999 *(Continued)*

		Judgement comment: participants and personnel were not masked. We felt that lack of masking was unlikely to lead to performance bias for this outcome.
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Quote: "... visual acuity examination with refraction by a trained ophthalmic technician, who was masked to the patients' status in the trial" Page 575, methods. Judgement comment: However, patients were not masked which may influence visual acuity assessment.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "Initial and serial fluorescein angiograms were read in a masked manner by two observers...." Page 575, methods. Judgement comment: Lack of masking of participants is unlikely to influence this outcome.
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: 27 participants were entered in the trial with a mean follow-up of 15 months (range of 7 to 32 months). In the radiation group mean follow-up was 17 months. In the group assigned to observation the mean follow-up was 16 months. In the methods it states that participants *"were followed on a 3-month basis"* however it was not clear from the report why different participants had different lengths of follow-up.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no access to study protocol or trial registry entry.

Ciulla 2002

Study characteristics	
Methods	Parallel group RCT Probably one eye per person as refer to "affected eye", unclear how selected
Participants	Country: USA. Number of participants (eyes) randomised: 37 (?37) Number of participants (eyes) excluded after randomisation: 7 (?7) Number of participants (eyes) analysed: 24 (?24) (at 12 months) 13 (?13) (at 24 months) Average age: 71 years (median) (range NR) Sex: 38% women. Inclusion criteria: • subfoveal CNV due to age-related macular degeneration • subjective visual acuity impairment of affected eye of less than 6 months' duration • best-corrected visual acuity of the affected eye of 20/40 and 20/400 Exclusion criteria: • inability to maintain steady fixation with either eye • preexisting microangiopathy, including diabetic retinopathy • media opacity sufficient to preclude examination and follow-up • inability to give informed consent • inability to comply with follow-up regimen

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Ciulla 2002 *(Continued)*

Interventions	Intervention: (n=30*) • External beam radiation therapy (2 fractions of 8 Gy) • Duration: 2 days Comparator: (n=10*) • Sham External beam radiation therapy (not described *37 participants recruited but *"No data were recovered from seven subjects owing to four baseline discrepancies, one off-protocol treatment due to equipment failure, and two discontinuations before the first treatment".* NR which groups these 7 lost to follow-up belonged to.
Outcomes	Primary: NR Secondary: NR Reported (but data available only for visual acuity): • Visual acuity (logMAR, ETDRS chart) • CNV size and leakage • Subretinal haemorrhage Follow-up: 3, 6, 12, 18 and 24 months
Notes	Date conducted: June 1998 to January 2000 Sources of funding: *"Supported by the Indiana Lions Club, by an unrestricted grant from Research to Prevent Blindness, Inc, New York, New York, and by an Intercampus Research Grant from Research and University Graduate School, Indiana University and the Pearl Vision Foundation. Doctor Ciulla is a recipient of a Career Development Award from Research to Prevent Blindness, Inc."* Conflict of interest: NR Trial id: NR Other information: *"Recruitment was halted at 37 subjects for ethical reasons regarding randomization to sham treatment when Food and Drug Administration approval of Visudyne (Novartis Ophthalmics, Duluth, Georgia, USA) was anticipated."*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: not reported.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not reported.
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "A randomized, sham-controlled clinical trial" Description of study in title, abstract and methods page 905. Quote "Masked assessment of angiography and analysis of visual acuity between groups were performed" Page 905. Judgement comment: although this statement is not very clear as to whether the measurement of visual acuity was masked as the control group had sham irradiation we have assumed that measurement of visual acuity was masked.

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Ciulla 2002 *(Continued)*

Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Quote: "Masked assessment of angiography and analysis of visual acuity between groups were performed" Page 905. Judgement comment: although this statement is not very clear as to whether the measurement of visual acuity was masked as the control group had sham irradiation we have assumed that as the trial was sham-controlled participants and personnel were masked.
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "Masked assessment of angiography and analysis of visual acuity between groups were performed" Page 905. Judgement comment: although this statement is not very clear as to whether the measurement of visual acuity was masked as the control group had sham irradiation we have assumed that measurement of visual acuity was masked.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "Masked assessment of angiography and analysis of visual acuity between groups were performed" Page 905. Judgement comment: although this statement is not very clear as to whether the measurement of visual acuity was masked as the control group had sham irradiation we have assumed that measurement of visual acuity was masked.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 37 subjects enrolled in this investigation [...] no data were recovered from seven subjects owing to four baseline discrepancies, one off-protocol treatment due to equipment failure, and two discontinuations before the first treatment." Page 906. Judgement comment: no information was given as to which treatment group these exclusions belonged to and only data for 30 participants analysed. At 12 months, 16/20 and 7/10 participants in treatment and control group respectively seen (page 906, table 1). No reason was given for this loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no access to study protocol or trial registry entry.

Eter 2002

Study characteristics	
Methods	Parallel group RCT One eye per person, unclear how eye selected
Participants	Country: Germany. Number of participants (eyes) randomised: 45 (45) Number of participants (eyes) excluded after randomisation: NR Number of participants (eyes) analysed: 42(42) Average age: 74 years (range 45 to 92) Sex: 57% women. Inclusion criteria: • Age 45+ years • Classic/occult subfoveal CNV • Informed consent

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Eter 2002 *(Continued)*

- No prior radiation treatment to head
- No vascular eye disease
- Neovascularisation as a results of AMD alone
- No prior treatment of AMD.

Exclusion criteria: NR

Interventions	Intervention: (n=27)* • Exernal beam radiation therapy (10 fractions of 2 Gy) • Duration: "3 times a week" so assume duration is approximately 3 weeks Comparator: (n=15)* • Observation * This is the number followed up. Original allocation not reported; 3 participants lost to follow-up.
Outcomes	Primary: NR Secondary: NR Reported: • Visual acuity (logMAR) • Membrane size Follow-up: 6 months
Notes	Date conducted: NR Sources of funding: NR Declaration of interest: NR Trial id: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Forty-five eyes of 45 patients [...] were assigned randomly in a ratio of 2:1 to either radiation treatment or observation." Page 14 Judgement comment: authors did not describe how the allocation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not reported.
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Judgement comment: masking was not mentioned in the report. We judged that participants and personnel were probably not masked which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Judgement comment: the control group was observation only so we have assumed that participants and personnel were not masked. We felt that lack of masking was unlikely to lead to performance bias for this outcome.

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Eter 2002 *(Continued)*

Blinding of outcome assessment (detection bias) Visual acuity	High risk	Judgement comment: as control group was observation only we have assumed visual acuity assessment not masked.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Judgement comment: control group was observation only we have assumed participants and personnel were not masked. We felt that lack of masking was unlikely to lead to performance bias for this outcome.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Although 45 patients were randomized to either treatment or follow-up, 27 patients in the radiation group and 15 patients in the control group could be enrolled in the study. Three patients were lost to follow-up because motivation for further examinations was low and because they needed to be accompanied by relatives due to their age and visual acuity." Page 14. Judgement comment: no information was given as to which group the excluded participants belonged. No information was given as to numbers examined at six month follow-up.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no access to study protocol or trial registry entry.

INTREPID 2013

Study characteristics	
Methods	Parallel group RCT One eye per person, unclear how selected
Participants	Country: Europe, multi-centre Number of participants (eyes) randomised: 230 (230) Number of participants (eyes) excluded after randomisation: 0 Number of participants (eyes) analysed: 230 (230) Average age: 74 years (range NR) Sex: 69% women Inclusion criteria: • Neovascular age-related macular degeneration (AMD) diagnosed within the previous 3 years, have received at least three injections with Lucentis® (ranibizumab) or Avastin® (bevacizumab) within the previous year, and have the need for treatment with anti–vascular endothelial growth factor (VEGF) therapy due to increased fluid or persistent cysts on optical coherence tomography (OCT), or leakage on fluorescein angiography (FA). • Total lesion size of <12 disc areas and a CNV lesion with the greatest linear dimension of <6 mm, but not greater than 3 mm from the centre of the fovea to the furthest point on the lesion perimeter. • Distance from the cent er of the fovea to the nearest edge of the optic disc should be not less than 3 mm. • At least 50 years of age • Women must be post-menopausal for ≥1 year or surgically sterilized, or a pregnancy screen must be performed prior to the study and a reliable form of contraception approved by the investigator must be maintained during the study • Best corrected visual acuity of 75 to 25 letters in the study eye and at least 20 letters in the fellow eye.

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INTREPID 2013 *(Continued)*

	Exclusion criteria: • CNV due to causes other than AMD, including ocular histoplasmosis syndrome, angioid streaks, multifocal choroiditis, choroidal rupture, or pathologic myopia (spherical equivalent ≥ –8 diopters) • Axial length of <20 mm or >26 mm • Previously diagnosed with diabetes mellitus and/or a haemoglobin A1c (HbA1c) value of >6.5%, and with retinal findings consistent with diabetic retinopathy • Prior or concurrent therapies for AMD, including submacular surgery, subfoveal thermal laser photocoagulation (with or without photographic evidence), transpupillary thermotherapy (TTT), ocular photodynamic therapy, radiation therapy to the head or neck in the study eye. • Previous posterior vitrectomy, or any surgery in the study eye within 6 months or YAG (yttrium-aluminum-garnet) capsulotomy within 3 months prior to the screening visit. • Intravitreal device in the study eye. • Concomitant disease in the study eye including uveitis, acute ocular or periocular infection, retinal vasculopathies (including retinal vein occlusions, etc.) or intraocular pressure ≥30 mmHg uncontrollable with medications. • History of rhegmatogenous retina detachment, optic neuritis, or intraocular tumours in the study eye. • Inadequate pupillary dilation or significant media opacities in the study eye, including cataract, which may interfere with visual acuity or the evaluation of the posterior segment. • Likely to need cataract surgery during the 2-year study period
Interventions	Intervention 1: (n=75) • External beam (stereotactic) radiation therapy (1 fraction of 16Gy) • Ranibizumab (0.5mg) day 0 and as needed (pro re nata, PRN) Intervention 1: (n=75) • External beam (stereotactic) radiation therapy (1 fraction of 24 Gy) • Ranibizumab (0.5mg) day 0 and PRN Comparator: (n=80) • Sham radiation • Ranibizumab (0.5mg) day 0 and PRN External beam radiation therapy was delivered by the IRay Radiotherapy System (Oraya Therapeutics, Newark, CA)). "To be eligible for additional ranibizumab injections, participants had to meet 1 or more of the following retreatment criteria: a 100-m increase in central subfield thickness from the lowest previous OCT measurement, new or increased macular hemorrhage documented by fundus photographs, or a 5-letter or more decrease in BCVA since the last visit or the baseline BCVA, with disease activity, for example, persistent or increased fluid on OCT or leakage on FA."
Outcomes	Primary outcome: • Number of PRN ranibizumab injections administered over 52 weeks. Secondary were: • Mean change in best-corrected visual acuity (BCVA) based • Loss of fewer than 15 letters, • Gain of 15 letters or more • Gain of 0 letters or more, • Time from mandatory ranibizumab injection at day 0 to the first PRN ranibizumab injection • Change in total lesion size on fluorescein angiography, and change in CNV lesion size on FA. S • Adverse events (AEs) and serious AEs (SAEs).

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INTREPID 2013 *(Continued)*

	Follow-up: Every 4 weeks to 52 weeks
Notes	Full study name: IRay in Conjunction with Anti-VEGF Treatment for Patients with Wet AMD (INTREPID) Date conducted: December 2009 to April 2013 Sources of funding: Oraya Therapeutics Declaration of interest: Quote “Oraya Therapeutics participated in the design of the study, conducting the study, data collection, data management, data analysis, and review of the manuscript.” All authors report support from Oraya therapeutics Trial id: NCT01016873

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A dynamic randomization algorithm was used to balance for the following: whether the patient exhibited a dry macula at any time after previous anti-VEGF therapy, whether the diagnosis of wet AMD was fewer than 6 months, or 6 months or more before study entry, and whether the baseline (day 0) visual acuity score was 54 letters or fewer, or 55 letters or more." Page 1894 Quote: “A stochastic minimization algorithm,25 using a minimization probability parameter of 0.80, was used for dynamic randomization. The balance used for the minimization algorithm changed 3 times in the study, but the final intended ratio at the end of enrolment achieved the intended 2:1:2:1 distribution.“ Page 1894
Allocation concealment (selection bias)	Low risk	Quote: "Treatment assignment and dose were acquired through a secure, password-protected website." Page 1894
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "All patients and study personnel, including personnel from the sponsor, were masked to active or sham treatments." Page 1894 Quote “The operator of the SRT device was not masked to whether the participant was receiving the 16-Gy or 24-Gy dose because the treatment times differed. However, all study personnel, including the operator, were masked to whether active or sham treatment was delivered for the chosen dose.“ Page 1895
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Quote: "All patients and study personnel, including personnel from the sponsor, were masked to active or sham treatments." Page 1894 Quote: “The operator of the SRT device was not masked to whether the participant was receiving the 16-Gy or 24-Gy dose because the treatment times differed. However, all study personnel, including the operator, were masked to whether active or sham treatment was delivered for the chosen dose.“ Page 1895
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "All patients and study personnel, including personnel from the sponsor, were masked to active or sham treatments." Page 1894
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "All patients and study personnel, including personnel from the sponsor, were masked to active or sham treatments." Page 1894

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INTREPID 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: similar numbers followed up to one year: 16Gy 74/75 24 Gy 72/75 and sham 79/80.
Selective reporting (reporting bias)	Low risk	Judgement comment: outcomes on trial register same as in published report

Jaakkola 2005

Study characteristics	
Methods	Parallel group RCT One eye per person for most participants, 2 participants had 2 eyes enrolled
Participants	Country: Finland. Number of participants (eyes) randomised: 86 (88) Number of participants (eyes) excluded after randomisation: 0 Number of participants (eyes) analysed: 82 (84) (at 12 months) 76 (78) at 3 years Average age: 76 years . Sex: 60% women Inclusion criteria: • Recent angiographically proven exudative AMD with subfoveal CNV • Best-corrected visual acuity (VA) of 20/200 or better • Size of the lesion had to be no larger than 6 disc areas and not exceed the boundaries of the active area of the plaque to be used • At least ambulatory vision had to be present in the other eye Exclusion criteria: • Age 55 years or younger • Uncontrolled or advanced glaucoma, diabetes, cataract precluding angiography, or • estimation that surgery would be required within 3 years
Interventions	Intervention: (n=43, 43 eyes) • Episceral brachytherapy (Sr^{90} plaques*) Comparator: (n=43, 45 eyes) • Observation **"Two different plaque types were used. Plaque I had a diameter of 8 mm and delivered a dose of 15 Gy at a depth of 1.75 mm in 54 minutes. With plaque II, the corresponding values were 4 mm, 12.6 Gy, and 11 minutes"*
Outcomes	Primary: • Visual acuity (ETDRS) Secondary: • Contrast sensitivity

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Jaakkola 2005 *(Continued)*

	• Changes in the macula Follow-up: 6, 12, 24 and 36 months
Notes	Date conducted: 1996 to 2000 Sources of funding: Eye Foundation, Helsinki, Finland, and Friends of the Blind (De Blindas Vänner—Sokeain Ystävät ry), Helsinki, Finland. Declaration of interest: Reported "none". Trial id: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: not reported.
Allocation concealment (selection bias)	Unclear risk	Quote: "Treatment allocation was performed by envelope randomization within CNV categories, as described below." Page 568. Judgement comment: not really enough information to judge whether this was done properly.
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Quote: "Visual acuity was measured [...] by an examiner masked against the treatment given to the patient." Page 569 Judgement comment: participants were probably not masked which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Quote: "The angiograms were evaluated in a masked manner...." Page 569. Judgement comment: participants were unmasked but performance bias unlikely to affect the lesion size
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Quote: "Visual acuity was measured [...] by an examiner masked against the treatment given to the patient." Page 569 Judgement comment: participants were not masked which may have affected measurement of visual acuity.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "The angiograms were evaluated in a masked manner...." Page 569
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 43/43 participants in radiotherapy group seen at 12 months however it was also reported that two participants had died in the interim. 39/43 participants in the control group (91%) seen at 12 months. Flow chart was confusing because at 6 months it was reported that four participants refused and at 12 months it was reported one participant refused. However same numbers 39/43 seen at both time points. Page 569, figure 1.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no access to study protocol or trial registry entry.

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Kacperek 2001

Study characteristics	
Methods	Parallel group RCT Unclear how many eyes
Participants	Country: UK Number of participants (eyes) randomised: 58 (?) Number of participants (eyes) excluded after randomisation: NR Number of participants (eyes) analysed: unclear Average age: 76 years (range 56 to 86) Sex: 61% women (but reported for intervention arm only) Inclusion criteria: • Aged 50+ with subfoveal CNV (classic) and evidence of AMD e.g. drusen • Visual acuity > 6/60 Exclusion criteria: • Diabetes • Severe hypertension • Retinal vascular disease • Myopia
Interventions	Intervention: (n=38) • External beam radiation therapy (4 fractions of 4.5 Gy) • Duration: NR Comparator: (n=20) • Observation.
Outcomes	Primary: NR Secondary: NR Reported: • Visual acuity (ETDRS) • Contrast sensitivity and angiography mentioned but not reported Follow-up: 3, 6 and 12 months
Notes	Date conducted: NR Sources of funding: NR Declaration of interest: NR Trial id: NR

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Kacperek 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote:"Patients [...] were randomised to between treatment and control". Page 7 Judgement comment: authors did not describe how the allocation schedule was generated.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not reported.
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Judgement comment: masking was not mentioned in the report. We judged that participants and personnel were probably not masked which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Judgement comment: participants were unmasked but performance bias unlikely to affect the lesion size.
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Judgement comment: no masking was reported and there was no sham intervention in the control group.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	High risk	Judgement comment: no masking was reported and there was no sham intervention in the control group.
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: initial allocation was 38 participants in the treatment arm and 20 for the control arm. 27 participants in treatment arm versus 20 in control arm reported at 12 months. No information on people not seen.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no access to study protocol or trial registry entry.

Kobayashi 2000

Study characteristics	
Methods	Parallel group RCT One eye per person, chosen by participant and clinician
Participants	Country: Japan Number of participants (eyes) randomised: 101 (101) Number of participants (eyes) excluded after randomisation: NR Number of participants (eyes) analysed: 85 (85) at all time points to 24 months Average age: 72 years (range 60 to 89) Sex: 64% women Inclusion criteria:

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Kobayashi 2000 *(Continued)*

	• Unsuitable for laser photocoagulation under the Macular Photocoagulation Study criteria, (2) newly formed or exacerbated choroidal neovascular membranes (e.g., within 3 months) • Visual acuity of 0.5 (25/50) or worse • Age of 60 years of more Exclusion criteria: • Pre-existing ocular disease (i.e., glaucoma, severe myopia, chronic inflammatory disease, or neoplastic disorders) • Systemic disorders (diabetes, uncontrolled hypertension) or a known life-threatening disease.
Interventions	Intervention: (n=51) • External beam radiation therapy (10 fractions of 2 Gy) • Duration: 14 days Comparator: (n=50) • Observation
Outcomes	Primary: NR Secondary: NR Reported: • Visual acuity (ETDRS) • Area of CNV (FFA) • Safety Follow-up: 2 weeks, 1, 3, 6, 9, 12, 18 and 24 months
Notes	Date conducted: NR Sources of funding: Hyogo Prefecture and Hyogo Medical Society, Hyogo, Japan. Declaration of interest: NR Trial id: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "One eye of each of the 101 patients was prospectively randomized to receive radiotherapy or no treatment." and "Within 24 hours after enrollment, the patients were randomized by means of computer-generated numbers; patients assigned 0 received low-dose radiotherapy and those assigned 1 received no treatment." Page 618
Allocation concealment (selection bias)	Low risk	Quote: "The treating physician (HK) was unaware of the patients' randomization state". Page 618
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Judgement comment: masking of participants was not mentioned in the report. We judged that participants were probably not masked which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias)	Low risk	Judgement comment: masking of participants was not mentioned in the report. We judged that participants were probably not masked but performance bias unlikely to affect the lesion size.

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Kobayashi 2000 *(Continued)*

Lesion size on fluorescein angiography		
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Quote: "Assessment of outcomes, including visual acuity, angiographic interpretation, and assessment of complications and adverse events, was performed in a masked fashion." Page 618 Judgement comment: participants were not masked which may have affected measurement of visual acuity.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "Assessment of outcomes, including visual acuity, angiographic interpretation, and assessment of complications and adverse events, was performed in a masked fashion." Page 618
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "The overall complete follow-up rate was 84.1% (85/101) (Table 1 and Figure 1). there was no significant difference between the two groups; the complete follow-up rate was 88.2% (45/51) and 80.0% (40/50) in the treatment group and control group, respectively. Six treated patients and 10 untreated patients were not evaluated, because five patients died with intercurrent disease, six patients were to ill or frail to attend, and it was not possible to contact five patients. Page 619, results. Judgement comment: although follow-up was over 80% there were some differences between the intervention and comparator group.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no access to study protocol or trial registry entry.

Marcus 2001

Study characteristics	
Methods	Parallel group RCT One eye per person, unclear how eye selected
Participants	Country: USA. Number of participants (eyes) randomised: 83 (83) Number of participants (eyes) excluded after randomisation: NR Number of participants (eyes) analysed: 70 (70) (at 12 months) Average age: 76 years (range NR) Sex: 61% women Inclusion criteria: Active subfoveal CNV secondary AMD Older than 48 years of age Visual acuity $\geq$ 20/400 Clinical and angiographic evidence of a choroidal neovascular membrane Exclusion criteria: Previous laser treatment

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Marcus 2001 *(Continued)*

	Choroidal neovascularisation due to other causes Retinal vascular diseases e.g. diabetes; previous ocular, orbital or periorbital radiation; likely candidates for chemotherapeutic agents
Interventions	Intervention: (n=41) • External beam radiation therapy (7 fractions of 2 Gy) • Duration: 7 working days Comparator: (n=42) • Sham treatment (1 session) • Duration: 1 day
Outcomes	Primary: • Distance visual acuity (logMAR, ETDRS) Secondary: • Contrast sensitivity (Pelli-Robson chart) • Appearance of fundus Follow-up: specified as 3, 6, 12, 24 weeks, and every 6 months to 4 years but only data up to 12 months reported.
Notes	Date conducted: February 1995 to September 1998 Sources of funding: Grant from Research to Prevent Blindness, New York and grants from the Knights Templar Educational Foundation of Georgia. Declaration of interest: NR Trial id: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization incorporated blocking, which is recommended any time patient recruitment extends for a long period of time. Blocks of size 2 or 4 were assigned randomly, and a separate random permutation was used to assign the 2 treatments to the blocks." Page 172
Allocation concealment (selection bias)	High risk	Quote "A randomization schedule was printed and sent to the radiology team, who then sequentially allocated the patients to the sham or actual radiation treatments". Page 172 Judgement comment: allocation schedule was clearly not concealed.
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "The patient, examining ophthalmologist, and ophthalmic technician were unaware of the assignment to observation or radiation treatment groups." Page 172 Judgement comment: study was sham-controlled.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The patient, examining ophthalmologist, and ophthalmic technician were unaware of the assignment to observation or radiation treatment groups." Page 172

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Marcus 2001 *(Continued)*

Lesion size on fluorescein angiography		
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "The patient, examining ophthalmologist, and ophthalmic technician were unaware of the assignment to observation or radiation treatment groups." Page 172
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "The patient, examining ophthalmologist, and ophthalmic technician were unaware of the assignment to observation or radiation treatment groups." Page 172
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: differences in follow-up between groups and follow-up less than 80% in the control group. Radiation group n=41. 37 (90%) seen at one year, 4 with missing data. Control n=42. 33 (79%) seen at one year, 6 with missing data, 3 withdrawn. Page 175, table 2.
Selective reporting (reporting bias)	High risk	Judgement comment: follow-up to 4 years but only data up to 12 months reported.

MERLOT 2016

Study characteristics	
Methods	Parallel group RCT One eye per person, if both eyes eligible participant chose which eye would be treated
Participants	Country: UK (24 hospitals) Number of participants (eyes) enrolled: 363 (363) Number of participants (eyes) excluded after randomisation: Age: 77 years (range 56 to 96) Sex: 60% women Inclusion criteria: • Subfoveal choroidal neovascularisation associated with wet age-related macular degeneration. • Retinal Angiomatous Proliferation (RAP) lesions not directly involving the fovea must be associated with contiguous foveal leakage demonstrated on fundus examination, OCT, or fluorescein angiography • Received anti-VEGF induction treatment, defined as the first three months of anti-VEGF therapy. Following this induction period, participants must have received at least 4 additional injections of Lucentis® in no more than 12 months preceding enrolment, or 2 additional injections of Lucentis® in no more than 6 months preceding enrolment, given on an as needed basis • Aged 50 years or older and met the NICE treatment criteria for Lucentis® therapy, i.e. all of the following circumstances must apply in the eye to be treated: the best-corrected visual acuity is between 6/12 and 6/96 (24 to 69 ETDRS letters) there is no permanent structural damage to the central fovea the lesion size is less than or equal to 12 disc areas in greatest linear dimension there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes) Exclusion criteria: • Has not been treated in accordance with NICE guidance • Visual acuity worse than 6/96 at the time of study enrolment

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MERLOT 2016 *(Continued)*

- Prior or concurrent subfoveal CNV therapy with agents, surgery or devices (other than Macugen®, Avastin®, or Lucentis®) including thermal laser photocoagulation (with or without photographic evidence), photodynamic therapy, intravitreal or subretinal steroids, and transpupillary thermotherapy (TTT)
- Subfoveal scarring
- Active concomitant disease in the study eye, including uveitis, presence of pigment epithelial tears or rips, acute ocular or periocular infection;
- Previously diagnosed with Type 1 or Type 2 Diabetes Mellitus or retinal findings consistent with Type 1 or Type 2 Diabetes Mellitus;
- Advanced glaucoma (greater than 0.8 cup:disk) or intraocular pressure ≥ 30 mmHg in the study eye
- Previous glaucoma filtering surgery in the study eye
- Inadequate pupillary dilation or significant media opacities in the study eye, including cataract, which may interfere with visual acuity or the evaluation of the posterior segment;
- Current vitreous haemorrhage in the study eye
- History of rhegmatogenous retinal detachment or macular hole in the study eye;
- CNV due to causes other than AMD, including known or suspected idiopathic polypoidal choroidal vasculopathy (IPCV), ocular histoplasmosis syndrome, angioid streaks, multifocal choroiditis, choroidal rupture, or pathologic myopia (spherical equivalent ≥ 8 Dioptre or axial length ≥ 25mm);
- Any intraocular surgery in the study eye within 12 weeks prior to the screening visit, with the exception of cataract surgery
- Previous cataract surgery within 2 months prior to enrolment into the study;
- Known serious allergies to fluorescein dye used in angiography;
- Known sensitivity or allergy to Lucentis®;
- Previous radiation therapy to the eye, head or neck;
- An intravitreal device or drug in the study eye;
- Any other condition, which in the judgment of the investigator would prevent completing the study (e.g. documented diagnosis of dementia or serious mental illness);
- Current participation in another drug or device clinical trial, or participation in such a clinical trial within the last year;
- History of use of drugs with known retinal toxicity, including: chloroquine (Aralen - an anti-malarial drug), hydroxychloroquine (Plaquenil), phenothiazines, chlorpromazine (Thorazine), thioridazine (Mellaril), fluphenazine (Prolixin), perphenazine (Trilafon), and trifluoperazine (Stelazine)
- Unwilling or unable to return for scheduled treatment and follow-up examinations for three years
- Women must be post-menopausal more than 1 year unless surgically sterilised

Interventions	Intervention: (n=244) • Epimacular brachytherapy, Strontium-90 (24 Gy) • Ranibizumab (0.5mg) monthly as required Comparator: (n=119) • Ranibizumab (0.5mg) monthly as required
Outcomes	Primary: • Mean change in ETDRS best-corrected visual acuity at 24 months • Number of re-treatment injections of Lucentis® per participant, per year Secondary: • Percentage losing < 15 ETDRS letters • Percentage gaining ≥ 0 ETDRS letters • Percentage gaining ≥ 15 ETDRS letters • Change in total lesion size by fluorescein angiography • Change in total CNV size by fluorescein angiography • Foveal thickness measured using OCT.

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MERLOT 2016 *(Continued)*

	Follow-up: 24 months Information from clinicaltrials.gov
Notes	Date conducted: November 2009 to January 2012 Sources of funding: Quote "NeoVista (Fremont, CA) provided unrestricted research funding but had no role in data collection, analysis, or in the preparation or review of this manuscript" Declaration of interest: Authors reported financial support from NeoVista Trial id: NCT01006538

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Online electronic randomization was undertaken immediately after eligibility was confirmed by recruiting sites using a commercial system (MedSciNet, Stockholm, Sweden)."
Allocation concealment (selection bias)	Low risk	Quote: "Online electronic randomization was undertaken immediately after eligibility was confirmed by recruiting sites using a commercial system (MedSciNet, Stockholm, Sweden)."
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Judgement comment: participants and personnel were not masked which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Unclear risk	Judgement comment: participants and personnel were not masked and it is unclear whether this would have affected lesion size (for example, by differential treatment with anti-VEGF).
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "VA testing and macular imaging (which were the most commonly used criteria to necessitate ranibizumab retreatment) were undertaken by masked assessors."
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "VA testing and macular imaging (which were the most commonly used criteria to necessitate ranibizumab retreatment) were undertaken by masked assessors."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: at 12 months, 13/363 (3.3%) participants were missing visual acuity measurements. These were imputed using multiple imputation. The ranibizumab retreatment injection analysis also included all participants but no correction was made for participants who withdrew early. Fluorescein angiography and OCT data were not available for 26 (7.2%) and 19 (5.2%) of eyes respectively.
Selective reporting (reporting bias)	Low risk	Judgement comment: outcomes on trials registry entry were reported

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Osmanovic 2017

Study characteristics	
Methods	Parallel group RCT One eye included in study; if both eyes were eligible, then the eye with the worse VA was treated.
Participants	Country: USA Number of participants (eyes) randomised: 30 (30) Number of participants (eyes) excluded after randomisation: 8 (8) Number of participants (eyes) analysed: 22 (22) Average age: 77 years (range not reported) Sex: 59% women Inclusion criteria: • newly diagnosed neovascular AMD or evidence of recurrent active neovascular AMD. • subfoveal or juxtafoveal choroidal neovascularization identified by fundus fluorescein angiography • best-corrected visual acuity of 6/12 to 6/120 (20/40 to 20/400) Exclusion criteria: • additional macular or optic nerve comorbidities, • history of diabetes mellitus • history of prior head and neck radiation • intravitreal anti-VEGF treatment in the study eye within the 6 weeks before enrolment Eyes with newly diagnosed neovascular AMD were recruited preferentially, but eyes with less than three prior intravitreal anti-VEGF therapies and with recurrent active neovascular AMD were considered for study enrolment.
Interventions	Intervention 1: (n=7) • External beam radiation therapy (2 fractions of 12 Gy) Intervention 2: (n=7) • External beam radiation therapy (2 fractions of 8 Gy) Comparator: (n=8) • Sham radiation therapy (2 sessions) Duration: 24 hours apart. Radiation was administered 2 weeks to 6 weeks after enrolment and administration of the first study intravitreal anti-VEGF therapy. All participants received anti-VEGF therapy (either ranibizumab 0.5mg or bevacizumab 1.25mg in 0.05mL). Quote "For sham radiation, a thermoplastic head mask was used to immobilize the head and eyelid retractors were used to remove the eyelids from the sham radiation field. Eye fixation was monitored and maintained for the sham radiation. The sham treatment was identical to the actual proton beam treatment except no treatment planning was performed and no radiation was administered."
Outcomes	Outcomes specified on clinical trials registry

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Osmanovic 2017 *(Continued)*

Primary outcome:

- Incidence of severe vision loss from radiation retinopathy or other causes defined as number of eyes with 3 or more lines of vision loss from baseline at 12 and 24 months

Secondary (12 and 24 months):

- number of anti-VEGF therapy [Time Frame: Month 12 and 24]
- number of eyes with 3 or more lines of visual acuity gain from baseline
- number of eyes with radiation retinopathy or papillopathy

Outcomes reported in the publication (12 months)

- Mean best-corrected visual acuity
- Cataract progression
- Lesion area of CNV membrane
- Resolution of leakage on FA
- OCT measurements, mean CRT
- Size of PED
- Number of intravitreal anti-VEGF treatments
- Radiation retinopathy or papillopathy
- Severe vision loss (loss of BCVA of 3 or more Snellen lines)
- Adverse arteriothromboembolic events

Notes

Full study name: ProspectiveTrial of Proton Beam Combined With Anti-VEGF Therapy for Exudative Age-related Macular Degeneration (AMD) (PBAMD2)

Date conducted: September 2010 to January 2015

Sources of funding: Quote: "Supported in part by a Strategic CTSI grant from UCSF (K.M.) and Research to Prevent Blindness Unrestricted Grant."

Declaration of interest: Quote: "The authors made the following disclosures: L.M.: Contracted research- Genentech, Allergan, Roche/Novartis. A.M.: Contracted research Genentech, Allergan, Roche/Novartis; Honoraria Genentech. S.S.P.: Contracted research e Genentech, Allergan, Roche/Novartis; Honoraria Genentech."

Trial id: NCT01213082

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was conducted by the unmasked study coordinator using a sequential coin toss, first to determine sham versus PBT, then 1 of 2 doses of PBT if subject was randomized to PBT."
Allocation concealment (selection bias)	High risk	Quote: "The randomization was conducted by the unmasked study coordinator using a sequential coin toss, first to determine sham versus PBT, then 1 of 2 doses of PBT if subject was randomized to PBT. Because this is a small study, the total enrollment of each study group was roughly equal throughout the study with variations in enrollment number limited to within 2 subjects relative to the other study groups during the study after accounting for any subjects who were excluded from the study after study enrollment."

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Osmanovic 2017 *(Continued)*

		Judgement comment: Allocation was unmasked.
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "Both the examining study ophthalmologist and study subject were masked to study group randomization until study completion. The radiation oncologist and the randomizing study coordinator were unmasked to study randomization and did not participate in follow-up study examination and anti-VEGF retreatment decision making. For the interim 1-year data analysis, 1 investigator (E.M.) not involved in follow-up study eye examination and anti-VEGF retreatment decision making was unmasked." Judgement comment: sham radiation in the control group.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Quote: "Both the examining study ophthalmologist and study subject were masked to study group randomization until study completion. The radiation oncologist and the randomizing study coordinator were unmasked to study randomization and did not participate in follow-up study examination and anti-VEGF retreatment decision making. For the interim 1-year data analysis, 1 investigator (E.M.) not involved in follow-up study eye examination and anti-VEGF retreatment decision making was unmasked." Judgement comment: sham radiation in the control group.
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "Both the examining study ophthalmologist and study subject were masked to study group randomization until study completion. The radiation oncologist and the randomizing study coordinator were unmasked to study randomization and did not participate in follow-up study examination and anti-VEGF retreatment decision making. For the interim 1-year data analysis, 1 investigator (E.M.) not involved in follow-up study eye examination and anti-VEGF retreatment decision making was unmasked." Judgement comment: sham radiation in the control group.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "Both the examining study ophthalmologist and study subject were masked to study group randomization until study completion. The radiation oncologist and the randomizing study coordinator were unmasked to study randomization and did not participate in follow-up study examination and anti-VEGF retreatment decision making. For the interim 1-year data analysis, 1 investigator (E.M.) not involved in follow-up study eye examination and anti-VEGF retreatment decision making was unmasked." Judgement comment: sham radiation in the control group.
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: 22/30 participants followed up to one year (73%) and not clear follow-up by group in published study report. On clinical trials registry follow-up was lower in the control group: at 24 months 6/12 (50%) in 24Gy group, 7/11 (64%) and 4/11 (in sham irradiation group (36%). Reason for loss to follow-up given on trials registry was "lost to follow-up".
Selective reporting (reporting bias)	High risk	Judgement comment: differences between outcomes pre-specified on the clinical trials registry and outcomes reported in the paper.

RAD 1999

Study characteristics	
Methods	Parallel group RCT

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RAD 1999 *(Continued)*

	One eye per person, unclear how selected
Participants	Country: Germany Number of participants (eyes) randomised: 205 (205) Number of participants (eyes) excluded after randomisation: 11 (11) (participant DNA) Number of participants (eyes) analysed: 183 (183) at 12 months Average age: 74 years (range 54 to 88) Sex: 60% women 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	Intervention: (n=101) • External beam radiation therapy (8 fraction of 2 Gy) • Duration: 10 days Comparator: (n=104) • Sham irradiation (8 fractions of 0Gy)
Outcomes	Primary outcome: • Change in visual acuity between baseline and 12 months (logMAR, ETDRS) Secondary: NR Reported: • Safety Follow-up: 6 and 12 months
Notes	Full study name: The Radiation Therapy for Age-related Macular Degeneration (RAD) Study Date conducted: February 1996 to October 1997 Sources of funding: Deutsche Forschungsgemeinschaft (DFG), Bonn, Germany (grant # Vo 437/3-1), and by the State of Baden-Wu¨rttemberg, Heidelberg, Germany (grant # 88/94). Declaration of interest: NR Trial id: NR
Risk of bias	

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RAD 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization list was compiled generating random numbers using the statistical analysis system SAS, version 6.12." Page 2240
Allocation concealment (selection bias)	Low risk	Quote: "To ensure concealment, external randomization by telephone was performed by the Biostatistics and Data Centre, Heidelberg, Germany." Page 2240
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote:"Patients in the placebo group were similarly planed and placed at the linear accelerator for 8 fractions with a dose of 8 x 0Gy. The machine noise during irradiation was simulated, and the technicians were instructed not to inform the patient about the mode of treatment. The sham treatment method was spread out over an identical time course as the radiation treatment." Page 2240 Quote "To ensure masking of patients and ophthalmologists, only the respective departments of radiation therapy were informed about treatment allocation." Page 2240
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Quote "To ensure masking of patients and ophthalmologists, only the respective departments of radiation therapy were informed about treatment allocation." Page 2240 Quote: "All angiograms were read by reviewers masked to treatment assignments." Page 2240
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "Patients in the placebo group were similarly planed and placed at the linear accelerator for 8 fractions with a dose of 8 x 0Gy. The machine noise during irradiation was simulated, and the technicians were instructed not to inform the patient about the mode of treatment. The sham treatment method was spread out over an identical time course as the radiation treatment." Page 2240 Quote: "To ensure masking of patients and ophthalmologists, only the respective departments of radiation therapy were informed about treatment allocation." Page 2240
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "All angiograms were read by reviewers masked to treatment assignments." Page 2240
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: radiation group 88/101 (87.1%) completed study 7 of these protocol deviations. Sham therapy group 95/104 (91.3%) completed study. Detailed information given on loss to follow-up. Page 2241, figure 1.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no access to study protocol or trial registry entry.

SFRADS 2002

Study characteristics	
Methods	Parallel group RCT

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SFRADS 2002 *(Continued)*

	One eye per person, unclear how selected
Participants	Country: UK Number of participants (eyes) randomised: 203 (203) Number of participants (eyes) excluded after randomisation: 4 (4) Number of participants (eyes) analysed: 184 (at 12 months) 174 (at 24 months) Average age: 75 years (range NR) Sex: 57% women Inclusion criteria: • Aged 60+ • Subfoveal CNV Visual acuity 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	Intervention: (n=99)* • External beam radiation therapy (6 fractions of 2 Gy) • Duration: 6 consecutive working days Comparator: (n=100)* • Observation Duration: *One control participant treated and included in intervention group; 4 protocol violations excluded.
Outcomes	Primary outcome: • Loss of visual acuity at 12 and 24 months (logMAR, EDTRS) Secondary: • Near visual acuity (Bailey-Lovie chart) • Contrast sensitivity • Complications • Quality of life Follow-up: 3, 6, 12 and 24 months
Notes	Full study name: Subfoveal Radiotherapy Study (SFRADS) Date conducted: November 1995 to July 1998 Sources of funding: Project grant G9404235 from Medical Research Council of the UIK. Declaration of interest: NR

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SFRADS 2002 *(Continued)*

Trial id: ISRCTN84737434

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "To ensure balance within each of the 3 centers, the randomization was blocked." Hart et al, page 1031.
Allocation concealment (selection bias)	Low risk	Quote: "The randomization code was kept at the coordinating center (Belfast) and released by telephone on receipt of patient details."Hart et al, page 1030/1031.
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Quote: "The optometrists who undertook visual assessments were unaware of the treatment status of the patients; however, neither the treating physicians nor the patients were masked". Hart et al, page 1030 Judgement comment: participants and personnel were not masked which may have affected the visual acuity outcome.
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Unclear risk	Judgement comment: outcome not reported so far.
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Quote: "The optometrists who undertook visual assessments were unaware of the treatment status of the patients; however, neither the treating physicians nor the patients were masked". Hart et al, page 1030 Judgement comment: although visual acuity assessment was masked to treatment group, physicians and patients were not. It is possible that an individual's performance on the visual acuity test could be influenced by their perceptions as to which treatment they received.
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Unclear risk	Judgement comment: outcome not reported so far.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 101 allocated to treatment 102 to observation. 93/101 and 91/100 seen at 12 months. Not very good documentation for reasons for no follow-up.
Selective reporting (reporting bias)	Low risk	Judgement comment: trials registry outcomes reported

Valmaggia 2002

Study characteristics

Methods	Parallel group RCT One eye per person, unclear how selected
Participants	Country: Switzerland.

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Valmaggia 2002 *(Continued)*

	Number of participants (eyes) randomised: 161 (161) Number of participants (eyes) excluded after randomisation: NR Number of participants (eyes) analysed: 150 (6 months) 139 (12 months) 137 (18 months) Average age: 75 years (range NR) Sex: 58% women Inclusion criteria: • Subfoveal CNV in AMD • Rapid worsening of visual acuity, a central scotoma, or metamorphopsia Exclusion criteria: • Foveal haemorrhage • Severe haemorrhage or serous PED impeding measurement of CNV • Preexisting ocular disease (glaucoma, severe myopia, diabetic retinopathy).
Interventions	Intervention 1: (n=52) • External beam radiation therapy (4 fractions of 4 Gy) Intervention 2: (n=57) • External beam radiation therapy (4 fractions of 2 Gy) Comparator: (n=52) • External beam radiation therapy (4 fractions of 0.25 Gy) Duration: 4 days.
Outcomes	Primary: NR Secondary: NR Reported: • BCVA (logMAR) • Reading ability • Radiation-associated side effects (ocular irritation, conjunctivitis, cataract, radiation retinopathy, radiation optic neuropathy) Follow-up: 6, 12 and 18 months
Notes	Date conducted: November 1994 to February 1999 Sources of funding: NR Declaration of interest: NR Trial id: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were stratified in four different subgroups according to the CNV type, size and duration of the symptoms" Page 522 Quote: "According to the stratification, patients were randomized and treated in the Department of Radiation-Oncology." Page 522

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Valmaggia 2002 *(Continued)*

		Judgement comment: not clear how the allocation schedule was generated.
Allocation concealment (selection bias)	Low risk	Quote: "The collaborators in the Department of Ophthalmology and patients were not aware of the applied radiation dose. Colleagues in the Department of Radiation-Oncology were only informed about the eye to be treated and the stratification code." Page 522.
Blinding of participants and personnel (performance bias) Visual acuity	Low risk	Quote: "The collaborators in the Department of Ophthalmology and patients were not aware of the applied radiation dose." Page 522
Blinding of participants and personnel (performance bias) Lesion size on fluorescein angiography	Low risk	Quote: "The collaborators in the Department of Ophthalmology and patients were not aware of the applied radiation dose." Page 522
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	Quote: "The collaborators in the Department of Ophthalmology and patients were not aware of the applied radiation dose." Page 522
Blinding of outcome assessment (detection bias) Lesion size on fluorescein angiography	Low risk	Quote: "The collaborators in the Department of Ophthalmology and patients were not aware of the applied radiation dose." Page 522
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: control group 44/52 (85%) seen at 12 months; 8Gy group 52/57 (91%) seen at 12 months; 16Gy group 43 (83%) seen at 12 months. Page 524, table 2.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no access to study protocol or trial registry entry.

AMD: age-related macular degeneration
ARM: age-related maculopathy
CNV: choroidal neovascularisation
CRT: central retinal thickness
ETDRS: Early Treatment of Diabetic Retinopathy Study
FFA: fundus fluorescein angiography
Gy: gray
NR: Not reported
OCT: optical coherence tomography
PDT: photodynamic therapy
PED: pigment epithelial detachment
PRN: pro re nata

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

Study	Reason for exclusion
Avila 2009	Not a randomised controlled trial.
Barak 2005	No control group.
Bergink 1995	Treatment groups probably not randomly allocated.

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Study	Reason for exclusion
Brown 1997	Treatment groups allocated sequentially.
Churei 2004	Treatment groups not randomly allocated.
Eter 2001	One eye treated and fellow eye served as a control. Unclear whether first eye treated randomly.
Friedrichsen 1996	Abstract only reporting two different doses of radiotherapy
Heier 2008	Avastin but not radiotherapy allocated randomly.
Honjo 1997	Treatment groups probably not randomly allocated.
Jackson 2012	Not a report of a randomised controlled trial
Mandai 1998	Treatment groups probably not randomly allocated.
Mandai 2000	Retrospective study - groups not allocated randomly.
Marcus 2004	Non-randomised dose escalation study.
Matsuhashi 1996	Treatment groups not allocated randomly.
Matsuhashi 2000	Treatment groups not allocated randomly. Control group consisted of people who had refused radiation or laser treatment.
NCT01833325	Single group assignment
Postgens 1997	Retrospective study - groups not allocated randomly.
Reichel 2007	All participants received radiotherapy, different regimen for anti-VEGF compared.
Saric 2001	Control group consisted of participants 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 (36 Gy). The study was continued as a non-randomised study and the reports did not distinguish randomised and non-randomised comparisons.
Zambarakji 2006	No untreated control group.

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

STAR (NCT02243878)

Study name	Stereotactic Radiotherapy for Wet AMD (STAR)
Methods	Parallel group RCT
Participants	Country: UK (10 hospitals) Estimated number of participants: 411 Ages: 50 years and above

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STAR (NCT02243878) *(Continued)*

<from clinicaltrials.gov>

Inclusion Criteria

1. *Participants must have neovascular AMD in the study eye, for which they have received at least 3 prior intravitreal injections of either bevacizumab (Avastin), aflibercept (Eylea), ranibizumab (Lucentis), or pegaptanib (Macugen).*
2. *Participants must have received an anti-VEGF injection in the study eye within 3 months prior to enrolment.*
3. *Participants must require treatment with anti-VEGF therapy at the time of enrolment, due to OCT evidence of subretinal fluid and/or cystoid macular oedema, and a macular volume that is greater than the 95th percentile of normal for the SD-OCT machines used in the investigational sites.*
4. *Participants must be at least 50 years of age.*

Exclusion Criteria

1. *Disciform scarring that involves the fovea, in the study eye.*
2. *Geographic atrophy that involves the fovea, or an area of geographic atrophy that is more than 500 microns in greatest diameter, immediately adjacent to the fovea, in the study eye.*
3. *Visual acuity worse than 6/96 (24 ETDRS letters) in the study eye.*
4. *Lesion size greater than 4 mm in greatest linear dimension, or greater than 2 mm from the centre of the fovea to the furthest point on the lesion perimeter.*
5. *Distance from the centre of the fovea to the nearest edge of the optic disc less than 3 mm in the study eye (this distance is confirmed by the Oraya SRT device software immediately prior to treatment).*
6. *An axial length of less than 20 mm, or greater than 26 mm, in the study eye.*
7. *Contraindication or sensitivity to contact lens application, including recurrent corneal erosions, in the study eye.*
8. *Type 1 or Type 2 diabetes mellitus.*
9. *Retinopathy in the study eye.*
10. *Prior or current therapies in the study eye for age-related macular degeneration, other than anti-VEGF agents, including submacular surgery, subfoveal thermal laser photocoagulation, photodynamic therapy (PDT), or transpupillary thermotherapy (TTT).*
11. *Presence of an intravitreal device in the study eye.*
12. *Previous radiation therapy to the study eye, head, or neck with the exception of radio-iodine treatment for hyperthyroidism, epimacular brachytherapy to the non-study eye, or Oraya SRT to the non-study eye.*
13. *Inadequate pupillary dilation or significant media opacities in the study eye, including cataract, which may interfere with visual acuity testing, the clinical evaluation of the posterior segment, or fundus imaging.*
14. *Likely to need cataract surgery in the study eye, within two years of enrolment.*
15. *Study eyes with CNV due to causes other than AMD, including presumed ocular histoplasmosis syndrome (POH), angioid streaks, multifocal choroiditis, choroidal rupture, and pathological myopia (greater than 8 Dioptres spherical equivalent). Participants with retinal angiomatous proliferation (RAP) or idiopathic polypoidal choroidal vasculopathy (IPCV) are not excluded.*
16. *Known allergy to intravenous fluorescein, ICG or intravitreal ranibizumab.*
17. *Intraocular surgery or laser-assisted in situ keratomileusis (LASIK) in the study eye within 12 weeks prior to enrolment.*
18. *Prior pars plana vitrectomy in the study eye.*
19. *Current participation in another interventional clinical trial, or participation in such a clinical trial within the last six months.*
20. *Unwilling, unable, or unlikely to return for scheduled follow-up for the duration of the trial.*
21. *Women who are pregnant at the time of radiotherapy.*
22. *Participants with an implantable cardioverter defibrillator (ICD) or pacemaker implant (or any implanted device) where the device labelling specifically contraindicates patients undergoing X-ray.*

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STAR (NCT02243878) *(Continued)*	23.*Any other condition, which in the judgment of the investigator, would prevent the participant from granting informed consent or completing the study, such as dementia, and mental illness (including generalized anxiety disorder and claustrophobia)*
Interventions	Intervention: • Stereotactic radiotherapy (16 Gy) • Intravitreal injections of 0.5 mg ranibizumab (1 dose at baseline, then as needed up to monthly, if predefined retreatment criteria are met) Comparator: • Sham stereotactic radiotherapy (0 Gy) • Intravitreal injections of 0.5 mg ranibizumab (1 dose at baseline, then as needed up to monthly, if predefined retreatment criteria are met)
Outcomes	<from clnicaltrials.gov> • *Primary Outcome Measures: Number of as required (prn) ranibizumab injections during the first 24 months* • *Secondary Outcome Measures: Mean Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity (VA) at 24 months.*
Starting date	December 2014 to October 2022
Contact information	Timothy Jackson t.jackson1@nhs.net
Notes	www.starstudy.org.uk www.clinicaltrials.gov/ct2/show/NCT02243878 www.isrctn.com/ISRCTN12884465

DATA AND ANALYSES

Comparison 1. Radiation therapy versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Loss of 3 or more lines best-corrected visual acuity lost at 12 months	8	811	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.64, 1.04]
1.2 Three or more lines visual acuity lost at 24 months	4	654	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.63, 0.97]
1.3 Change in BCVA at 12 months	10	883	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.17, -0.03]
1.3.1 Change in visual acuity	7	771	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.16, -0.02]
1.3.2 Final value	3	112	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.41, 0.08]

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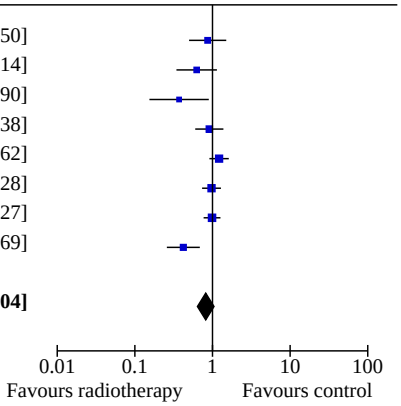
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.4 Change in BCVA at 24 months	6	516	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.15, -0.03]
1.5 Change in contrast sensitivity	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.5.1 12 months	2	267	Mean Difference (IV, Fixed, 95% CI)	0.15 [0.05, 0.25]
1.5.2 24 months	2	257	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.00, 0.22]
1.6 Contrast sensitivity raw data	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.6.1 12 months	1	83	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.38, -0.06]
1.6.2 24 months	1	82	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.41, -0.03]

Analysis 1.1. Comparison 1: Radiation therapy versus control, Outcome 1: Loss of 3 or more lines best-corrected visual acuity lost at 12 months

	Radiotherapy		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
AMDRT 2004	13	31	15	31	10.2%	0.87 [0.50 , 1.50]	
Bergink 1998	11	34	15	29	9.3%	0.63 [0.34 , 1.14]	
Char 1999	4	14	10	13	5.7%	0.37 [0.15 , 0.90]	
Jaakkola 2005 (1)	21	43	22	41	13.1%	0.91 [0.60 , 1.38]	
Marcus 2001	30	37	22	33	16.4%	1.22 [0.91 , 1.62]	
RAD 1999	45	88	50	95	16.6%	0.97 [0.73 , 1.28]	
SFRADS 2002	53	93	52	90	17.3%	0.99 [0.77 , 1.27]	
Valmaggia 2002	20	95	22	44	11.5%	0.42 [0.26 , 0.69]	
Total (95% CI)		**435**		**376**	**100.0%**	**0.82 [0.64 , 1.04]**	
Total events:	197		208				



Heterogeneity: Tau² = 0.07; Chi² = 20.41, df = 7 (P = 0.005); I² = 66%
Test for overall effect: Z = 1.61 (P = 0.11)
Test for subgroup differences: Not applicable

Footnotes
(1) Brachytherapy

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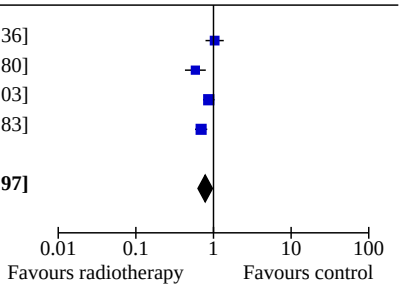
Analysis 1.2. Comparison 1: Radiation therapy versus control, Outcome 2: Three or more lines visual acuity lost at 24 months

Study or Subgroup	Radiotherapy Events	Radiotherapy Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Jaakkola 2005	30	41	29	41	22.6%	1.03 [0.79 , 1.36]
Kobayashi 2000 (1)	23	45	35	40	20.3%	0.58 [0.43 , 0.80]
SFRADS 2002	61	87	71	88	28.9%	0.87 [0.73 , 1.03]
Valmaggia 2002	90	181	94	131	28.2%	0.69 [0.58 , 0.83]
Total (95% CI)		**354**		**300**	**100.0%**	**0.78 [0.63 , 0.97]**
Total events:	204		229			

Heterogeneity: Tau² = 0.03; Chi² = 10.93, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 2.26 (P = 0.02)
Test for subgroup differences: Not applicable



Footnotes
(1) Brachytherapy

Analysis 1.3. Comparison 1: Radiation therapy versus control, Outcome 3: Change in BCVA at 12 months

Study or Subgroup	MD	SE	Radiation therapy Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Change in visual acuity						
Char 1999	-0.32	0.1696	14	13	3.7%	-0.32 [-0.65 , 0.01]
Jaakkola 2005 (1)	-0.137	0.077816	42	41	10.8%	-0.14 [-0.29 , 0.02]
Kobayashi 2000	-0.196	0.063467	45	40	13.0%	-0.20 [-0.32 , -0.07]
Marcus 2001	0.075	0.079	37	33	10.6%	0.07 [-0.08 , 0.23]
RAD 1999	-0.02	0.063484	88	95	13.0%	-0.02 [-0.14 , 0.10]
SFRADS 2002	-0.06	0.055	93	91	14.5%	-0.06 [-0.17 , 0.05]
Valmaggia 2002	-0.1213	0.0579	95	44	14.0%	-0.12 [-0.23 , -0.01]
Subtotal (95% CI)			**414**	**357**	**79.5%**	**-0.09 [-0.16 , -0.02]**

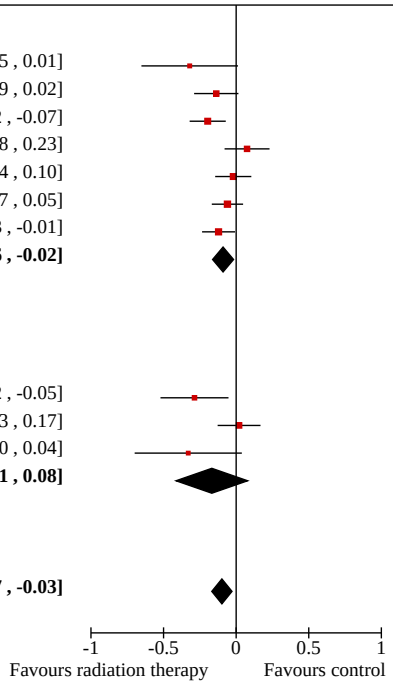
Heterogeneity: Tau² = 0.00; Chi² = 11.16, df = 6 (P = 0.08); I² = 46%
Test for overall effect: Z = 2.45 (P = 0.01)

1.3.2 Final value						
AMDLRTSG 2003	-0.287	0.1195	30	21	6.3%	-0.29 [-0.52 , -0.05]
Anders 1998	0.02	0.0753	19	18	11.1%	0.02 [-0.13 , 0.17]
Ciulla 2002	-0.33	0.1883	16	8	3.1%	-0.33 [-0.70 , 0.04]
Subtotal (95% CI)			**65**	**47**	**20.5%**	**-0.17 [-0.41 , 0.08]**

Heterogeneity: Tau² = 0.03; Chi² = 6.47, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 1.33 (P = 0.18)

Total (95% CI)			**479**	**404**	**100.0%**	**-0.10 [-0.17 , -0.03]**

Heterogeneity: Tau² = 0.01; Chi² = 17.64, df = 9 (P = 0.04); I² = 49%
Test for overall effect: Z = 2.77 (P = 0.006)
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%



Footnotes
(1) Brachytherapy

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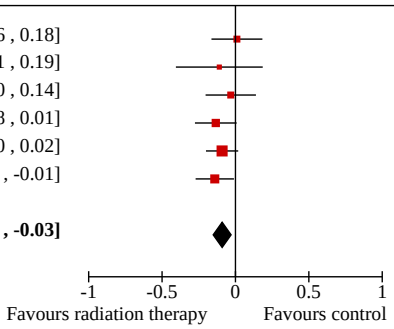
Analysis 1.4. Comparison 1: Radiation therapy versus control, Outcome 4: Change in BCVA at 24 months

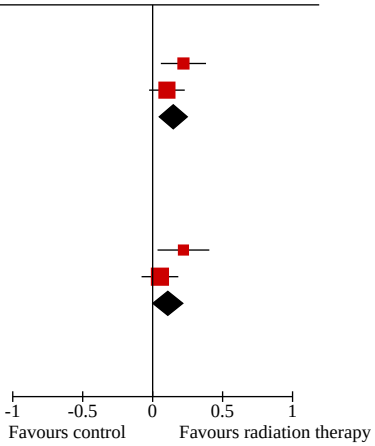
Study or Subgroup	MD	SE	Radiation therapy Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Anders 1998	0.01	0.0885	14	12	12.3%	0.01 [-0.16 , 0.18]
Ciulla 2002	-0.11	0.1509	6	5	4.2%	-0.11 [-0.41 , 0.19]
Jaakkola 2005	-0.032	0.0875	41	41	12.6%	-0.03 [-0.20 , 0.14]
Kobayashi 2000	-0.134	0.0724	45	40	18.4%	-0.13 [-0.28 , 0.01]
SFRADS 2002	-0.091	0.056	87	88	30.7%	-0.09 [-0.20 , 0.02]
Valmaggia 2002	-0.1409	0.0666	94	43	21.7%	-0.14 [-0.27 , -0.01]
Total (95% CI)			**287**	**229**	**100.0%**	**-0.09 [-0.15 , -0.03]**

Heterogeneity: Tau² = 0.00; Chi² = 2.69, df = 5 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.92 (P = 0.003)
Test for subgroup differences: Not applicable



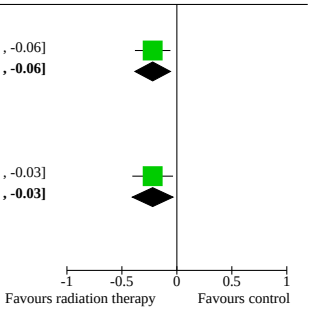
Analysis 1.5. Comparison 1: Radiation therapy versus control, Outcome 5: Change in contrast sensitivity

Study or Subgroup	MD	SE	Radiation therapy Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 12 months						
Jaakkola 2005	0.22	0.08235	42	41	38.4%	0.22 [0.06 , 0.38]
SFRADS 2002	0.102	0.065	93	91	61.6%	0.10 [-0.03 , 0.23]
Subtotal (95% CI)			**135**	**132**	**100.0%**	**0.15 [0.05 , 0.25]**
Heterogeneity: Chi² = 1.27, df = 1 (P = 0.26); I² = 21%						
Test for overall effect: Z = 2.89 (P = 0.004)						
1.5.2 24 months						
Jaakkola 2005	0.22	0.09443	41	41	33.5%	0.22 [0.03 , 0.41]
SFRADS 2002	0.052	0.067	87	88	66.5%	0.05 [-0.08 , 0.18]
Subtotal (95% CI)			**128**	**129**	**100.0%**	**0.11 [0.00 , 0.22]**
Heterogeneity: Chi² = 2.11, df = 1 (P = 0.15); I² = 53%						
Test for overall effect: Z = 1.98 (P = 0.05)						
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%						



Analysis 1.6. Comparison 1: Radiation therapy versus control, Outcome 6: Contrast sensitivity raw data

Study or Subgroup	Radiation Mean [log units]	Radiation SD [log units]	Radiation Total	Control Mean [log units]	Control SD [log units]	Control Total	Weight	Mean Difference IV, Fixed, 95% CI [log units]
1.6.1 12 months								
Jaakkola 2005 (1)	0.17	0.37	42	0.39	0.38	41	100.0%	-0.22 [-0.38 , -0.06]
Subtotal (95% CI)			**42**			**41**	**100.0%**	**-0.22 [-0.38 , -0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.67 (P = 0.008)								
1.6.2 24 months								
Jaakkola 2005 (1)	0.26	0.34	41	0.48	0.5	41	100.0%	-0.22 [-0.41 , -0.03]
Subtotal (95% CI)			**41**			**41**	**100.0%**	**-0.22 [-0.41 , -0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.33 (P = 0.02)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%								



Footnotes
(1) Change (decrease) in mean contrast sensitivity from baseline (nb Mann Whitney U test)

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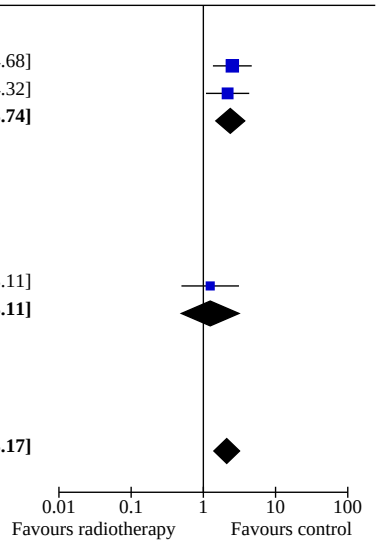
Comparison 2. Radiation therapy with anti-VEGF versus anti-VEGF alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Three or more lines visual acuity lost at 12 months	3	1050	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [1.40, 3.17]
2.1.1 Epimacular brachytherapy	2	820	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [1.49, 3.74]
2.1.2 Stereotactic radiotherapy	1	230	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.50, 3.11]
2.2 Three or more lines visual acuity lost at 24 months	2	820	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [1.68, 3.39]
2.3 Change in BCVA at 12 months	4	1072	Mean Difference (IV, Random, 95% CI)	0.05 [-0.03, 0.13]
2.3.1 Epimacular brachytherapy	2	820	Mean Difference (IV, Random, 95% CI)	0.10 [0.05, 0.15]
2.3.2 External beam radiotherapy	2	252	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.09, 0.03]
2.4 Change in BCVA at 24 months	2	819	Mean Difference (IV, Random, 95% CI)	0.17 [0.11, 0.23]

Analysis 2.1. Comparison 2: Radiation therapy with anti-VEGF versus anti-VEGF alone, Outcome 1: Three or more lines visual acuity lost at 12 months

Study or Subgroup	Radiotherapy and anti-VEGF Events	Total	Anti-VEGF alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Epimacular brachytherapy						
CABERNET 2013 (1)	54	302	11	155	42.2%	2.52 [1.36 , 4.68]
MERLOT 2016 (1)	40	244	9	119	35.1%	2.17 [1.09 , 4.32]
Subtotal (95% CI)		**546**		**274**	**77.3%**	**2.36 [1.49 , 3.74]**
Total events:	94		20			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 3.66 (P = 0.0003)						
2.1.2 Stereotactic radiotherapy						
INTREPID 2013 (2)	14	150	6	80	22.7%	1.24 [0.50 , 3.11]
Subtotal (95% CI)		**150**		**80**	**22.7%**	**1.24 [0.50 , 3.11]**
Total events:	14		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**696**		**354**	**100.0%**	**2.11 [1.40 , 3.17]**
Total events:	108		26			
Heterogeneity: Chi² = 1.59, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 3.57 (P = 0.0004)						
Test for subgroup differences: Chi² = 1.49, df = 1 (P = 0.22), I² = 33.1%						



Footnotes
(1) Epimacular brachytherapy
(2) Stereotactic radiotherapy

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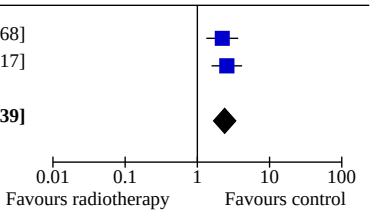
Analysis 2.2. Comparison 2: Radiation therapy with anti-VEGF versus anti-VEGF alone, Outcome 2: Three or more lines visual acuity lost at 24 months

Study or Subgroup	Radiotherapy and anti-VEGF Events	Total	Anti-VEGF alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CABERNET 2013 (1)	69	302	16	155	49.6%	2.21 [1.33 , 3.68]
MERLOT 2016 (1)	84	244	16	119	50.4%	2.56 [1.57 , 4.17]
Total (95% CI)		**546**		**274**	**100.0%**	**2.39 [1.68 , 3.39]**
Total events:	153		32			

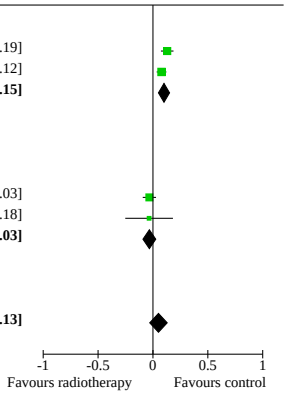
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 4.85 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) Epimacular brachytherapy

Analysis 2.3. Comparison 2: Radiation therapy with anti-VEGF versus anti-VEGF alone, Outcome 3: Change in BCVA at 12 months

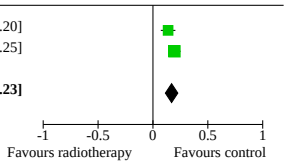
Study or Subgroup	Radiotherapy and anti-VEGF Mean [logMAR]	SD [logMAR]	Total	Anti-VEGF alone Mean [logMAR]	SD [logMAR]	Total	Weight	Mean Difference IV, Random, 95% CI [logMAR]
2.3.1 Epimacular brachytherapy								
CABERNET 2013	0.01	0.326	302	-0.12	0.278	155	29.6%	0.13 [0.07 , 0.19]
MERLOT 2016	0.096	0.216	244	0.018	0.194	119	31.6%	0.08 [0.03 , 0.12]
Subtotal (95% CI)			**546**			**274**	**61.2%**	**0.10 [0.05 , 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 1.99, df = 1 (P = 0.16); I² = 50%								
Test for overall effect: Z = 3.90 (P < 0.0001)								
2.3.2 External beam radiotherapy								
INTREPID 2013 (1)	-0.0012	0.1911	150	0.0314	0.238	80	29.1%	-0.03 [-0.09 , 0.03]
Osmanovic 2017	-0.175	0.25	14	-0.14	0.25	8	9.7%	-0.03 [-0.25 , 0.18]
Subtotal (95% CI)			**164**			**88**	**38.8%**	**-0.03 [-0.09 , 0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 1.10 (P = 0.27)								
Total (95% CI)			**710**			**362**	**100.0%**	**0.05 [-0.03 , 0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 16.11, df = 3 (P = 0.001); I² = 81%								
Test for overall effect: Z = 1.24 (P = 0.22)								
Test for subgroup differences: Chi² = 11.51, df = 1 (P = 0.0007), I² = 91.3%								



Footnotes
(1) Stereotactic

Analysis 2.4. Comparison 2: Radiation therapy with anti-VEGF versus anti-VEGF alone, Outcome 4: Change in BCVA at 24 months

Study or Subgroup	Radiotherapy and anti-VEGF Mean [logMAR]	SD [logMAR]	Total	Anti-VEGF alone Mean [logMAR]	SD [logMAR]	Total	Weight	Mean Difference IV, Random, 95% CI [logMAR]
CABERNET 2013 (1)	0.05	0.328	302	-0.088	0.35	155	44.9%	0.14 [0.07 , 0.20]
MERLOT 2016 (1)	0.224	0.314	243	0.028	0.218	119	55.1%	0.20 [0.14 , 0.25]
Total (95% CI)			**545**			**274**	**100.0%**	**0.17 [0.11 , 0.23]**
Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 1 (P = 0.19); I² = 42%								
Test for overall effect: Z = 5.89 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Epimacular brachytherapy

ADDITIONAL TABLES

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Table 1. Study characteristics

	Review edition study first included	Study name	Country	Funding	Number of people randomised	Number of eyes randomised	Note	Average age (years)	% female
1	2010	AMDLTRSG 2003	Japan	NR	69	69	Analysed	72	30
2	2010	AMDRT 2004	US	NIH	88	88		77	58
3	2004	Anders 1998	Germany	NR	76	76	unclear how many eyes	77	67
4	2004	Bergink 1998	The Netherlands	NR	74	74		75	56
5	2019	CABERNET 2013	US, Europe, Israel, South America	Manufacturer	494	494		77	68
6	2004	Char 1999	US	NGO	27	27		76	52
7	2004	Ciulla 2002	US	NGO	37	37	unclear how many eyes	71	38
8	2004	Eter 2002	Germany	NR	45	45		74	57
9	2019	INTREPID 2013	Europe	Manufacturer	230	230		74	69
10	2010	Jaakkola 2005	Finland	NGO	86	88		76	60
11	2004	Kacperek 2001	UK	NR	58	58	unclear how many eyes	76	61
12	2004	Kobayashi 2000	Japan	NGO	101	101		72	64
13	2004	Marcus 2001	US	NGO	83	83		76	61
14	2019	MERLOT	UK	Manufacturer	363	363		77	60

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Table 1. Study characteristics *(Continued)*

15	2019	Osmanovic 2017	US	NGO	30	30	77	59
16	2004	RAD 1999	Germany	GOV/NGO	205	205	74	60
17	2004	SFRADS 2002	UK	GOV	203	203	75	57
18	2004	Valmaggia 2002	Switzerland	NR	161	161	75	58
	Total				2430	2432	Median 76	Median 60

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Table 2. Type of choroidal neovascularisation

	Study	% classic	% occult	% mixed
1	AMDLRTSG 2003	NR		
2	AMDRT 2004	18 (predominantly classic)	21	61 (minimally classic)
3	Anders 1998	NR		
4	Bergink 1998	52	24	25
5	CABERNET 2013	39 (predominantly classic)	35	25
6	Char 1999	48	52	
7	Ciulla 2002	46	14	39
8	Eter 2002	37	Mixed/occult =	63.0
9	INTREPID 2013	NR		
10	Jaakkola 2005	40 ("a classic component")	52 ("occult no classic")	
11	Kacperek 2001	NR		
12	Kobayashi 2000	51	13	21
13	Marcus 2001	12	42	43
14	MERLOT 2016	12	75	12
15	Osmanovic 2017	50	50	
16	RAD 1999	38	62	
17	SFRADS 2002	52	2	43
18	Valmaggia 2002	57	43	

NR: Not reported

Table 3. Characteristics of the intervention and comparator

Study	Total dose (Gy)	Number of fractions	Control	Comments

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Table 3. Characteristics of the intervention and comparator *(Continued)*

Trials of external beam radiotherapy				
INTREPID 2013	24 and 16	1	Sham radiotherapy, ranibizumab (0.5mg and PRN)	Stereotactic radiotherapy; two arms receiving different radiation dose; all groups received ranibizumab (0.5mg and PRN)
Osmanovic 2017	24 and 16	2	Sham radiotherapy, ranibizumab or bevacizumab	Two arms receiving different radiation dose; all groups received ranibizumab or bevacizumab
Bergink 1998	24	4	Observation	
AMDRT 2004	20	5	Observation and sham radiotherapy	
Eter 2002	20	10	Observation	
Kobayashi 2000	20	10	Observation	
AMDLRTSG 2003	20	10	Observation	
Kacperek 2001	18	4	Observation	
Ciulla 2002	16	2	Sham irradiation	
RAD 1999	16	8	Sham irradiation (0 Gy)	
Marcus 2001	14	7	Sham irradiation	
SFRADS 2002	12	6	Observation	
Anders 1998	12	6	Observation	
Valmaggia 2002	8	4	Low dose irradiation (1 Gy)	
Char 1999	7.5	1	Observation	
Trials of brachytherapy (radiation source placed near the lesion)				
CABERNET 2013	24	1	Ranibizumab (0.5mg) 3 injections, over 3 months followed by quarterly injections	Epimacular brachytherapy; pars plana vitrectomy and placing of strontium 90/yttrium 90 applicator over AMD lesion. Intervention group also received 2 intravitreal injections of 0.5mg ranibizumab, one at the end of surgery and one 30 days later
MERLOT 2016	24	1	Ongoing PRN ranibizumab (0.5mg)	Epimacular brachytherapy; pars plana vitrectomy and placing of strontium 90 probe over AMD lesion to deliver required dose. All participants received PRN ranibizumab (0.5mg)
Jaakkola 2005	12 to 15	1	Observation	Plaque brachytherapy. One strontium 90 plaque delivered a dose of 15 Gy at a depth of 1.75 mm for 54 minutes but as this took too long another plaque was used which delivered a dose of 12.6 Gy at 4 mm depth for 11 minutes

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PRN: pro re nata

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Table 4. Subgroup analyses: three or more lines best-corrected visual acuity lost at 12 months

Subgroup		Radiotherapy		Control		Risk ratio	CI Start	CI End	I^2	Test for interaction (P-value)	Number of studies
		n	N	n	N						
All studies		197	435	208	376	0.82	0.64	1.04	66%		8
Dose	≤14Gy	107	239	106	180	0.73	0.44	1.20	84%	0.442	4
	>14Gy	90	196	102	196	0.90	0.73	1.10	0%		4
Type of CNV	Classic <50%	113	213	119	213	0.94	0.73	1.21	47%	0.261	5
	Classic 50% +	84	222	89	163	0.66	0.37	1.16	80%		3
Sham irradiation in the control group	No sham irradiation	102	215	114	204	0.83	0.64	1.07	32%	0.982	5
	Sham irradiation	95	220	94	172	0.82	0.49	1.39	86%		3

CI: confidence intervals CNV: choroidal neovascularisation

Table 5. Subgroup analyses: change in best-corrected visual acuity at 12 months

Subgroup		Radiotherapy N	Control N	Mean difference	CI Start	CI End	I^2	Test for interaction P value	Number of studies
All studies		479	404	-0.10	-0.17	-0.03	49%		10
Dose	≤14Gy	258	199	-0.05	-0.14	0.04	46%	0.134	5
	>14Gy	221	205	-0.15	-0.25	-0.05	42%		5
Type of CNV	Classic <50%	197	190	-0.09	-0.21	0.04	54%	0.901	5
	Classic 50%+	233	175	-0.12	-0.20	-0.04	24%		3
	% classic not reported	49	39	-0.12	-0.42	0.18	79%		2
Sham irradiation in the control group	No sham irradiation	243	224	-0.13	-0.22	-0.04	47%	0.321	6

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Table 5. Subgroup analyses: change in best-corrected visual acuity at 12 months *(Continued)*

Sham irradiation	236	180	-0.05	-0.17	0.06	53%	4

CI: confidence intervals CNV: choroidal neovascularisation

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Table 6. Adverse outcomes

	Study	Number of eyes randomised	Report
1	AMDLRTSG 2003	69	No comment on adverse effects in the report
2	AMDRT 2004	88	*"Adverse events were infrequent.By 12 months, one treated patient developed multiple cotton wool spots and retinal nonperfusion adjacent to the disc, possibly indicating radiation retinopathy. Visual acuity in this eye was 20/80 at baseline and 20/80 at 12 months. There were five deaths among AMDRT patients: four of which occurred among patients who did not receive EBR. Cataract surgery was performed on two patients, one in each treatment group. Six patients reported ocular dryness; four had not received EBR and two had received EBR"*
3	Anders 1998	76	Subretinal haemorrhage in 3 cases in both treatment and control groups. No other complications reported.
4	Bergink 1998	74	The prevalence of retinal abnormalities high in both treatment and control groups (72% and 71% respectively) but unlikely to be attributable to radiation.
5	CABERNET 2013	494	A higher proportion of the treatment group had serious ocular adverse event (54%) compared to the control group (18%). The majority of these adverse events were cataract. Overall 5% of the treatment group had device-related adverse events (17 cases); 10 of these cases were radiation retinopathy.
6	Char 1999	27	No comment on adverse effects in the report
7	Ciulla 2002	37	No comment on adverse effects in the report
8	Eter 2002	45	No comment on adverse effects in the report
9	INTREPID 2013	230	AEs similar across study arms and none attributed to radiation.
10	Jaakkola 2005	88	No comment on adverse effects in the report
11	Kacperek 2001	58	No comment on adverse effects in the report
12	Kobayashi 2000	101	Reported no radiation-associated adverse effects. 2 participants in treatment group "*complained of transient conjunctival injection that resolved within 2 weeks"* Cataract observed in 1 participant in treatment group but otherwise no evidence of cataract progression.
13	Marcus 2001	83	Reported no radiation-associated adverse effects. Cataract progression similar to treatment and control. 1 case of retinal detachment and 1 case of vitreous haemorrhage seen in radiation group
14	MERLOT 2016	363	In the radiotherapy plus ranibizumab group (n=244) there were 4 cases of reduced visual acuity, 1 vitreous haemorrhage, 3 retinal haemorrhage, 3 retinal detachment, 1 vision blurred, 1 endophthalmitis, 1 vitreous floaters,

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Table 6. Adverse outcomes *(Continued)*

			2 postoperative uveitis. In the ranibizumab only group (n=119) there was 1 case of reduced visual acuity and 1 case of retinal haemorrhage.
15	Osmanovic 2017	30	Reported no cases of: • severe vision loss • adverse arteriothromboembolic events • radiation retinopathy, neuropathy or anterior segment adverse effects. Cataract progression: Among the 13 phakic eyes (13 people) who completed the 12-month study follow-up, 4 had cataract progression (1 control, 2 from 16 GyE, 1 from 24 GyE). One eye receiving 16 GyE PBT underwent cataract extraction within the 1-year follow-up; however, this individual had moderately advanced cataract at baseline.
16	RAD 1999	205	Reported no radiation-associated adverse effects. Cataract developed in 7 (10.3%) radiation group, 12 (16%) control group) (P = 0.218). Dry eye symptoms in were recorded in 30 (40%) radiation group and 38 (45.2%) in control group (P = 0.525).4 deaths unrelated to radiation treatment, 3 in radiation group, 1 in control group
17	SFRADS 2002	203	Reported no radiation-associated adverse effects but *"transient disturbance of the precorneal tear film"* was noted in treated patients"
18	Valmaggia 2002	161	Reported no radiation-associated adverse effects.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Macular Degeneration
#2 MeSH descriptor Retinal Degeneration
#3 MeSH descriptor Neovascularization, Pathologic
#4 (macula* near degenerat*)
#5 (macula* near neovasc*)
#6 (retina* near degener*)
#7 (retina* near neovasc*)
#8 (choroid* near degener*)
#9 (choroid* near neovasc*)
#10 (maculopath*)
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 MeSH descriptor Radiotherapy
#13 (radiotherap* or radiat* or irradiat*)
#14 (teletherap* or tele-therap* or proton* or plaque)
#15 (external near beam)
#16 (external-beam)
#17 (#12 OR #13 OR #14 OR #15 OR #16)
#18 (#11 AND #17)

Appendix 2. MEDLINE Ovid search strategy

1 randomized controlled trial.pt.
2 (randomized or randomised).ab,ti.
3 placebo.ab,ti.
4 dt.fs.
5 randomly.ab,ti.

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6 trial.ab,ti.
7 groups.ab,ti.
8 or/1-7
9 exp animals/
10 exp humans/
11 9 not (9 and 10)
12 8 not 11
13 exp macular degeneration/
14 exp retinal degeneration/
15 exp retinal neovascularization/
16 exp choroidal neovascularization/
17 exp macula lutea/
18 (macula$ adj2 lutea).tw.
19 maculopath$.tw.
20 ((macul$ or retina$ or choroid$) adj3 degener$).tw.
21 ((macul$ or retina$ or choroid$) adj3 neovasc$).tw.
22 or/13-21
23 exp radiotherapy/
24 (radiotherap$ or radiat$ or irradiat$ or teletherap$ or proton$ or plaque).tw.
25 (external adj3 beam).tw.
26 or/23-25
27 22 and 26
28 12 and 27

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase Ovid search strategy

1 exp randomized controlled trial/
2 exp randomization/
3 exp double blind procedure/
4 exp single blind procedure/
5 random$.tw.
6 or/1-5
7 (animal or animal experiment).sh.
8 human.sh.
9 7 and 8
10 7 not 9
11 6 not 10
12 exp clinical trial/
13 (clin$ adj3 trial$).tw.
14 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15 exp placebo/
16 placebo$.tw.
17 random$.tw.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/
21 exp latin square design/
22 or/12-21
23 22 not 10
24 23 not 11
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control$ or propspectiv$ or volunteer$).tw.
29 or/25-28
30 29 not 10
31 30 not (11 or 23)
32 11 or 24 or 31
33 exp retina macula age related degeneration/
34 exp retina degeneration/

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35 exp neovascularization pathology/
36 ((macul$ or retina$ or choroid$) adj3 degener$).tw.
37 ((macul$ or retina$ or choroid$) adj3 neovasc$).tw.
38 maculopath$.tw.
39 or/33-38
40 exp radiotherapy/
41 (radiotherap$ or radiat$ or irradiat$ or teletherap$ or proton$ or plaque).tw.
42 (external adj3 beam).tw.
43 or/40-42
44 39 and 43
45 32 and 44

Appendix 4. LILACS search strategy

macula$ or retina$ or choroid$ and degenerat$ or neovasc$ and radiotherap$ or radiat$ or irradiat$ or teletherap$ or proton$ or plaque

Appendix 5. ISRCTN search strategy

(Macular Degeneration OR AMD OR nAMD OR ARMD) AND (radiotherapy OR radiation OR irradiation OR teletherapy OR proton OR plaque)

Appendix 6. ClinicalTrials.gov search strategy

(Macular Degeneration OR AMD OR nAMD OR ARMD) AND (radiotherapy OR radiation OR irradiation OR teletherapy OR proton OR plaque)

Appendix 7. WHO ICTRP search strategy

macular degeneration = Condition AND radiotherapy = Intervention

WHAT'S NEW

Date	Event	Description
1 May 2020	New citation required and conclusions have changed	Issue 8 2020: Four new studies included in update (CABERNET 2013; INTREPID 2013; MERLOT 2016; Osmanovic 2017)
1 May 2020	New search has been performed	Issue 8 2020: Electronic searches updated

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 4, 2004

Date	Event	Description
31 March 2010	New search has been performed	Issue 5 2010: Updated searches yielded 3 new trials.
31 March 2010	New citation required but conclusions have not changed	Review substantially updated including new assessment of risk of bias and preparation of summary of findings tables.
17 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: VC
Designing the review, writing the protocol: VC
Co-ordinating the review: VC, JE
Data collection for the review: JE, CI

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Screening search results: JE, EP
Organising retrieval of papers: JE
Screening retrieved papers against inclusion criteria: JE, EP
Appraising quality of papers: JE, CI
Abstracting data from papers: JE, CI
Writing to authors of papers for additional information: VC, JE
Obtaining and screening data on unpublished studies: JE
Data management for the review: JE
Entering data into RevMan: JE
Analysis of data: JE
Interpretation of data: All authors
Providing a clinical perspective: VC, TJ, EP
Writing the review: JE, VC, TJ, EP
Guarantor for the review: JE

DECLARATIONS OF INTEREST

JE: none known
CI: none known
TJ was a principal investigator and/or lead author in the CABERNET, MERLOT, MERITAGE and INTREPID studies. He leads an NIHR funded trial of the Oraya device. His employer received research payments for participants enrolled in commercial clinical trials of radiation devices used to treat wet AMD, and research grants or free use of radiation devices for investigator-initiated clinical trials of wet AMD. He is a consultant to Opthea and iLumens.
VC is consultant of Quantel Medical and is an employee of Boehringer Ingelheim. This publication expresses the opinion of the author (VC) and is not endorsed by Boehringer Ingelheim.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Guide Dogs for the Blind Association, UK
- National Institute for Health Research (NIHR), UK

  * Richard Wormald, Co-ordinating Editor for Cochrane Eyes and Vision (CEV) received financial support for his CEV research sessions (during this update) from the Department of Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology.
  * This review update was supported by the NIHR, via Cochrane Infrastructure funding to the CEV UK editorial base.

  The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review has been substantially updated since the original protocol was written and new methods, such assessment of risk of bias, GRADE assessment and summary of findings table, have been incorporated.

In previous versions of this review we considered loss of 3 and 6 lines of visual acuity. We felt that loss of 6 or more lines of visual acuity was not such a relevant outcomes now with the advent of anti-VEGF treatments and therefore made the decision to drop this outcome in the current review update. We have included change in best-corrected visual acuity instead.

Recent trials have considered the combination of anti-VEGF and radiotherapy. As a result, we have added in a new comparison "Radiotherapy combined with anti-VEGF versus anti-VEGF alone" and one additional outcome "number of injections of anti-VEGF". We have considered this as an outcome because one of the potential aims of radiotherapy would be to reduce the number of anti-VEGF injections required.

We also dropped the 6 month follow-up period and have focused on 12 and 24 months only.

In previous version of this review (Evans 2010) we assessed the potential impact of missing data in some detail and assessed the potential for selective outcome reporting using the ORBIT classification (Kirkham 2010). As these analyses did not point to any major sources of bias we have not updated them for the current version of this review.

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INDEX TERMS

Medical Subject Headings (MeSH)

Eye [radiation effects]; Macular Degeneration [*radiotherapy]; Radiation Injuries [complications]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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