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Systematic review of effectiveness of different treatments for childhood retinoblastoma

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The research reported in this monograph was commissioned by the HTA Programme as project number 03/63/01. The contractual start date was in May 2004. The draft report began editorial review in December 2004 and was accepted for publication in April 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Systematic review of effectiveness of different treatments for childhood retinoblastoma

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Objectives: To assess the clinical effectiveness of treatments for childhood retinoblastoma.
Data sources: Electronic databases were searched from inception to April 2004.
Review methods: Studies of participants diagnosed with childhood retinoblastoma, any interventions and all clinical outcomes were eligible for inclusion. Randomised and non-randomised controlled trials and cohort studies with clear comparisons between treatment groups were included. Methodological quality was assessed. A narrative synthesis was conducted. Where possible, studies assessing common interventions were grouped together, with prospective and retrospective studies grouped separately. Emphasis was placed on prospective studies.
Results: Thirty-one individual studies, from 42 publications, were included in the review. Apart from one non-randomised controlled trial, only comparative studies of observational design were available for any of the treatments. Four of the included studies were prospective and the remaining 27 were retrospective. Most of the studies were of radiotherapy or chemotherapy, with few studies available on enucleation or focal treatments such as brachytherapy, photocoagulation, cryotherapy and thermotherapy. The methodological quality was generally poor, with a high risk of bias in all included studies. The main problems were in relation to how treatment was allocated and lack of consideration of potentially confounding factors, such as initial disease severity, in the study design and data analysis. The evidence base for effectiveness of treatments for childhood retinoblastoma is extremely limited. Owing to the considerable limitations of the evidence identified, it was not possible to make meaningful and robust conclusions about the relative effectiveness of different treatment approaches for childhood retinoblastoma.
Conclusions: In the authors' opinion, the evidence base for the effectiveness of treatments for childhood retinoblastoma is not sufficiently robust to provide clear guidance for clinical practice. Ideally, good-quality randomised controlled trials (RCTs) assessing the effectiveness of different treatment options for childhood retinoblastoma are required. Research is required on all the treatments currently used for this condition. Where RCTs are not feasible, for ethical or practical reasons, only high-quality, prospective, non-randomised studies should be given consideration, owing to the generally higher risk of bias in retrospective studies. To reduce the risk of confounding due to allocation by clinical indication, studies should compare patients with similar disease severity rather than compare patients of mixed disease severities. Standardised outcomes should be agreed for use in studies assessing the effectiveness of treatment. These outcomes should encompass potential important adverse effects of treatment such as loss of visual acuity and cosmetic outcome, as well as beneficial effects.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Bilateral Tumour occurring in both eyes.

Brachytherapy A type of radiation treatment where radioactive materials (plaques or rods) are positioned in close proximity to the tumour.

Choroid The middle layer of the eye that contains blood vessels to nourish the eye.

Cryotherapy The use of freezing techniques to treat retinoblastoma

Enucleation Surgical removal of the eye.

Extraocular retinoblastoma Stage of retinoblastoma where the tumour has extended to tissues surrounding the eye, or beyond the eye to other parts of the body.

Fovea The centre of the macula responsible for the sharpest vision.

Germline The cells that give rise to the reproductive cells.

Germline (germinal) mutation A heritable alteration in the development of reproductive cells that can be transmitted to offspring.

Gray (Gy) The new SI unit of absorbed radiation dose, which has replaced the rad: 1 Gy is equivalent to 100 rad.

Hereditary retinoblastoma The genetic predisposition for retinoblastoma. It can be familial if there is existing family history or sporadic if there is a new germline mutation.

Intraocular retinoblastoma Stage of retinoblastoma that is confined to the retina or has extended to other parts of the eye, but has not extended beyond the eye.

Local extension Extension of the tumour to the sclera, choroid or optic nerve. If the tumour extends beyond these it is referred to as extraocular.

Macula The area of the retina responsible for central vision.

Metastasis Spread of disease to another part of the body.

Optic disc The point where the optic nerve enters the retina.

Optic nerve The part of the eye that contains nerve fibres responsible for transmitting information from the eye to the brain.

Rad A unit of absorbed dose of radiation which is being replaced by gray (Gy): 100 rad is equivalent to 1 Gy.

RB1 The retinoblastoma gene belongs to a class of genes that suppress the growth of tumours. An alteration in this gene during the development of retinal cells means that the cells continue to grow and a tumour develops.

Recurrent retinoblastoma The recurrence or progression of retinoblastoma following initial treatment.

Retina The inner, light-sensitive layer of the eye responsible for bringing images to the brain.

Retinoblastoma A malignant tumour of the retina.

Salvage therapy Treatment given when a tumour fails to respond to initial treatment.

Sclera The outer protective white coating of the eye.

Somatic Relevant to or characteristic of the body.

Somatic mutation An alteration in the somatic cells that is not present in the germline, so is not transferred to offspring.

continued

Glossary *continued*

Sporadic retinoblastoma Retinoblastoma that occurs randomly, that is, without a family history.

Subretinal seeding Small pieces of tumour that break off as the tumour grows into the subretinal space.

Trilateral retinoblastoma A midline intracranial or pineal tumour located in the pineal or suprasellar region of the brain. The tumour is independent and is not a result of direct spread of retinoblastoma.

Unilateral Tumour occurring in one eye.

Vitreous seeding Small pieces of tumour that break off as the tumour grows into the vitreous cavity.

List of abbreviations

ALS	anterior lens-sparing
ANOVA	analysis of variance
BSA	body surface area
CCG	Children's Cancer Group
CCSG	Children's Cancer Study Group
CI	confidence interval
^{60}Co	cobalt
CRD	Centre for Reviews and Dissemination
CT	computed tomography
EBRT	external beam radiotherapy
^{125}I	iodine
ICIRB	International Classification for Intraocular Retinoblastoma
^{192}Ir	iridium
MLB	modified lateral beam
MRI	magnetic resonance imaging
NA	not applicable
NED	no evidence of disease
NR	not reported
ns	not significant
NSCAG	National Specialised Commissioning Advisory Group
OR	odds ratio
POG	Pediatric Oncology Group
RCT	randomised controlled trial
RE	Reese–Ellsworth
RLS	relative lens-sparing
ROP	Registry of Ophthalmic Pathology
RR	relative risk
^{106}Ru	ruthenium
SD	standard deviation
SDS	standard deviation score
SE	standard error
SIR	standardised incidence ratio
SPT	second primary tumour
TEM	triethylene melamine

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Retinoblastoma is a malignant tumour of the retina and usually occurs in children under 2 years old. It is relatively rare, with an incidence of one case per 23,000 live births, and accounts for about 3% of all cancers occurring in children younger than 15 years in the UK. It is an aggressive tumour that can lead to loss of vision, and in extreme cases death, although cure rates in developed countries can be in excess of 90%.

Objective

The objective of this study was to assess the clinical effectiveness of treatments for childhood retinoblastoma.

Methods

Search

Seventeen electronic databases were searched from inception to April 2004 for studies published in any language. Internet searches were carried out and bibliographies of included articles were searched. Two reviewers independently assessed titles and abstracts and the full paper was obtained if either reviewer considered the reference potentially relevant. Two reviewers assessed the eligibility of full papers against the review inclusion criteria, with disagreements resolved by discussion and, if necessary, a third reviewer.

Inclusion and exclusion criteria

Studies of participants diagnosed with retinoblastoma at the age of 18 years or under were eligible for inclusion. Studies of adults were only included where childhood retinoblastoma was followed up into adulthood. Studies of mixed diagnoses were included if outcomes were reported separately for children with retinoblastoma. Any intervention, or combinations of intervention, and all clinical outcomes were eligible. Where controlled trials were not available, prospective and retrospective cohort studies with clear comparisons between treatment groups were eligible.

Data extraction

Data were extracted by one reviewer into structured summary tables and checked for accuracy by a second reviewer. Any disagreements were resolved by discussion and, if necessary, a third reviewer was involved.

Quality assessment

Each included study was assessed against a checklist for methodological quality of observational studies by one reviewer and checked by a second reviewer. Disagreements were resolved by discussion and, if necessary, a third reviewer was involved.

Synthesis

A narrative synthesis was conducted. Where possible, studies assessing common interventions were grouped together, with prospective and retrospective studies grouped separately. Emphasis was placed on prospective studies.

Results

Thirty-one individual studies, from 42 publications, were included in the review. Apart from one non-randomised controlled trial, only comparative studies of observational design were available for any of the treatments. Four of the included studies were prospective and the remaining 27 were retrospective. Most of the studies were of radiotherapy or chemotherapy, with few studies available on enucleation or focal treatments such as brachytherapy, photocoagulation, cryotherapy and thermotherapy.

The methodological quality was generally poor, with a high risk of bias in all included studies. The main problems were in relation to how treatment was allocated and lack of consideration of potentially confounding factors, such as initial disease severity, in the study design and data analysis.

The evidence base for effectiveness of treatments for childhood retinoblastoma is extremely limited. Owing to the considerable limitations of the

evidence identified, it was not possible to make meaningful and robust conclusions about the relative effectiveness of different treatment approaches for childhood retinoblastoma.

Conclusion

In the authors' opinion, the evidence base is not sufficiently robust to provide clear guidance for clinical practice.

Recommendations for research

Ideally, good-quality randomised controlled trials (RCTs) assessing the effectiveness of different treatment options for childhood retinoblastoma are required. Research is required on all the treatments currently used for this condition. Where RCTs are not feasible, for ethical or practical reasons, only high-quality, prospective, non-randomised studies should be given consideration, owing to the generally higher risk of bias in retrospective studies.

To reduce the risk of confounding due to allocation by clinical indication, studies should compare patients with similar disease severity rather than compare patients of mixed disease severities.

Standardised outcomes should be agreed for use in studies assessing the effectiveness of treatment. These outcomes should encompass potential important adverse effects of treatment such as loss of visual acuity and cosmetic outcome, as well as beneficial effects.

Chapter 1

Aim of the review

The National Specialised Commissioning Advisory Group (NSCAG) commissioned a systematic review on treatment outcomes in children with retinoblastoma. The purpose of the review is to provide the evidence base on clinical effectiveness for developing a robust audit of outcomes. The review builds on the work already done in a scoping review on the same topic, which was completed in October 2003.[1]

All interventions indicated for the treatment of childhood retinoblastoma were within the scope of the review, including (but not restricted to) enucleation, external beam radiotherapy, chemotherapy (EBRT), brachytherapy, cryotherapy, thermotherapy and photocoagulation.

Chapter 2
Background

Description of underlying health problem

Definition

Retinoblastoma is a malignant tumour of the retina and usually occurs in children under the age of 2 years. It is an aggressive tumour that can lead to loss of vision and, in extreme cases, death. However, the prognosis for vision and survival has significantly improved owing to more timely diagnosis and improved treatment methods.[2]

Retinoblastoma can be classified in three different but interrelated ways. These are: familial or sporadic, bilateral or unilateral and heritable or non-heritable.[3] Approximately 94% of newly diagnosed cases of retinoblastoma are sporadic, where there is no family history of disease, and the remaining 6% are familial, where there is a family history of disease. Retinoblastoma manifests as unilateral disease in 70–75% of cases and bilateral in the remaining cases. Approximately 40–50% of cases are hereditary and 50–60% are non-hereditary. It has been estimated that 15–20% of unilateral sporadic cases are hereditary caused by a germinal mutation, whereas the remaining cases are caused by somatic mutations that are confined to the retinal cells.[3] All cases of bilateral tumours are hereditary and are caused by germinal mutations. Patients with hereditary disease are more likely to have more than one tumour in one or both eyes, although in bilateral cases asymmetrical distribution between two eyes is common.[4] Approximately half of patients with germinal mutations will pass the predisposition for disease to their offspring.[3]

Patients with the hereditary form of retinoblastoma may be at increased risk of developing a second primary tumour (SPT) compared with those with the non-hereditary form.[5] The most common SPTs are osteosarcomas, although various other tumours, including melanomas, soft-tissue sarcomas and brain tumours, can occur.[4,6]

Staging

There are three stages of retinoblastoma: intraocular, extraocular and recurrent.

Intraocular retinoblastoma is the earliest stage of disease and the tumour is confined to the eye. The extent of intraocular disease progression varies. Intraocular retinoblastoma is one of the most curable of all childhood cancers, with 5-year survival rates in excess of 90%.[7–9] However, retinoblastoma is an aggressive tumour that can grow and spread rapidly. As the tumour grows it leaves the confines of the retina and spreads within the vitreous cavity or subretinal space. This can lead to seeding, retinal detachment, or extension to the choroid or scleral layers of the eye, to the optic nerve or to the anterior chamber.

Extraocular retinoblastoma is an advanced stage of disease where the tumour has extended beyond the sclera into orbital contents (orbital invasion) or beyond the optic nerve (optic nerve invasion) with direct extension to the CNS or distant metastases. Extraocular retinoblastoma is more prevalent in developing countries, primarily owing to delayed presentation of disease. The 5-year survival rate for patients with extraocular retinoblastoma has been estimated as less than 10%.[10]

Recurrent retinoblastoma is when the tumour has recurred or progressed following initial treatment. The recurrent tumour may be confined to the eye, tissues surrounding the eye or other parts of the body.

Staging systems have been developed to establish the severity of disease at presentation. They are used to provide a clinically meaningful method of predicting the outcome following primary treatment.[4] The most widely used and recognised system for intraocular retinoblastoma is the Reese–Ellsworth (RE) classification (see Appendix 1). This was developed in the 1960s to predict ocular salvage in intraocular tumours where EBRT was used to treat intraocular retinoblastoma.[11] The RE classification is based on the number, size and location of tumours, and the presence of vitreous seeding. However, the use of this classification has several limitations as it allows for patients with different numbers and sizes of tumours to be classified within the same group, yet their tumour response may differ.[12] With the development of alternative treatment options to avoid the late effects of use of EBRT, including

chemotherapy and focal treatment, the RE classification is regarded as less appropriate.[13] For example, treatment of RE group IIIa with cryotherapy has a more favourable prognosis than would be expected from the RE classification, and newer treatment modalities have improved the prognosis in cases of RE group Vb with vitreous seeding.[3] Alternative classification systems have since evolved. The improved prognosis associated with the use of newer treatment modalities was incorporated into the Essen classification,[14] which has been adopted by several European countries.[3] The International Classification for Intraocular Retinoblastoma (ICIRB) was recently developed specifically to account for advances in therapy (see Appendix 1).[4] In contrast to the RE, the ICIRB is based on the extent and location of the tumour and distinguishes between focal and diffuse vitreous seeding. It has been proposed that the ICIRB may improve the prediction of tumour response in patients classified as having the same stage of disease and will be a more informative staging system to guide treatment decisions.[15]

Several classification systems have been developed for extraocular retinoblastoma, and some have been developed for both intraocular and extraocular retinoblastoma. The classification systems used to stage extraocular retinoblastoma incorporate the degree of local extension, intracranial metastasis and haematological metastasis.[16,17]

Trilateral retinoblastoma

Patients with bilateral or hereditary disease are at risk of developing trilateral retinoblastoma. Trilateral retinoblastoma refers to a primary pineal tumour or an ectopic intracranial tumour located in the pineal or suprasellar region.[4] Trilateral retinoblastoma is an independent tumour that does not result from spread of intraocular retinoblastoma.[4,18,19] Trilateral retinoblastoma is relatively uncommon and is usually fatal.[19] Mortality from trilateral disease is high, and the median survival time from diagnosis of trilateral disease has been estimated as 9 months.[18] It is usually diagnosed approximately 2 years following the diagnosis of intraocular retinoblastoma[19,20] and may occur up to 11 years of age.[20] Patients who are asymptomatic for trilateral disease at the time of diagnosis have a better overall survival. This suggests that screening for trilateral disease using magnetic resonance imaging (MRI) in patients with bilateral and hereditary disease may improve prognostic outcome.[18,19]

Epidemiology

Retinoblastoma accounts for about 3% of cancers occurring in children younger than 15 years in the UK[9] and is the most common malignant ocular tumour of children, with an incidence of one case per 23,000 live births.[7] Approximately 20–30 new cases are diagnosed each year in England and Wales.[21] The incidence of retinoblastoma in northern Europe has remained stable over the past 50 years.[22,23] The National Registry of Childhood Tumours, a large population-based series of almost all childhood cancers diagnosed since 1962 in England, Scotland and Wales, estimated the average annual incidence of retinoblastoma from 1986 to 1995 as 4.6 cases per million children aged from birth to 14 years.[9] The annual UK incidence is estimated at 23.6 cases per million for children aged less than 1 year, decreasing to 8.2 and 0.6 for children aged 1–4 years and 5–9 years, respectively.[9] There is no predisposition for disease according to gender or race, and no tendency for either the right or left eye.[3]

The average age at diagnosis of retinoblastoma is 18 months. Bilateral cases are typically diagnosed earlier, at 12 months, whereas unilateral cases are diagnosed at 23 months.[3] Children with hereditary retinoblastoma are also typically diagnosed earlier than those with non-hereditary.[4]

Aetiology

Retinoblastoma can be hereditary or non-hereditary. The gene responsible for retinoblastoma is *RB1* and is located within the q14 band of chromosome 13, which controls retinal cell division.[24] In unaffected individuals *RB1* inhibits cell growth and acts as a tumour suppressor. Mutation or deletion of this gene during the development of retinal cells causes the retinal cells to continue dividing, leading to the formation of retinal tumours.

In hereditary retinoblastoma a mutation occurs in a primitive retinal cell in the presence of a predisposing first mutation in the germline, either as a new germline mutation sustained by the affected individual or from a mutation transmitted as an autosomal trait.[25,26] In patients with hereditary retinoblastoma the tumour manifests as either unilateral or bilateral disease, and all patients with bilateral tumours have the hereditary form of disease.

In non-hereditary retinoblastoma two somatic mutations occur in a single primitive retinal cell in

the absence of a predisposing germline mutation. This leads to the development of a solitary tumour. As the mutation is confined to the retinal cells the predisposition to disease is not transmitted to offspring. In patients with non-hereditary retinoblastoma the tumour always manifests as unilateral disease.[26]

Prognosis

The prognosis for both life and vision in patients with retinoblastoma has significantly improved during recent years, primarily owing to improved methods of diagnosis and treatment options.[27] Several clinical and histopathological factors have been associated with the prognostic outcome of patients with retinoblastoma.

Age and stage at diagnosis

Age at diagnosis and age at treatment have an effect on prognosis for life and vision. Patients diagnosed at younger than 2 years are thought to have a higher 3-year survival than those diagnosed at 2 years or older.[13,28] Children who are diagnosed at an older age usually present with a more advanced stage of disease and have an increased risk of extraocular extension and metastasis, which are the main causes of mortality in patients with retinoblastoma.[29] In addition, advanced tumours require a more intensive treatment regimen, which may adversely affect the amount of useful vision, or even survival of the patient.

Several tumour-related factors related to the stage of intraocular retinoblastoma affect survival and ocular salvage. These include the number and size of tumour(s), location, presence of seeding, retinal detachment and the extent of spread of retinoblastoma within the confines of the eye.[30,31] Patients with extraocular retinoblastoma are at increased risk of developing distant metastases.[27]

Heredity

Patients with the hereditary form of retinoblastoma who harbour the germline mutation are predisposed to significant long-term complications, in particular the development of SPTs. The most common is osteosarcoma, although others include soft-tissue sarcomas and brain tumours.[32] Patients with the genetic form of retinoblastoma are more likely to die from SPTs than the initial retinoblastoma.[4,28,33] Patients with the hereditary or bilateral disease are also susceptible to the development of trilateral retinoblastoma.[18]

Current service provision

Choice of treatment

Specialist oncology centres where multidisciplinary teams have developed treatment protocols are regarded as important for optimal management of patients owing to the rarity of the disease.[4] In the UK two designated centres have been established to provide rapid and accurate diagnosis, treatment and support of patients with retinoblastoma.[34] Patients with suspected retinoblastoma are referred to the designated centre, and undergo ocular and systemic examination to determine the stage of disease and presence of systemic involvement before starting treatment.

The aim of treatment is to reduce mortality, preserve useful vision and avoid long-term complications. The complexity of the disease process and therapeutic options mean that the management of retinoblastoma is invariably individualised with consideration of the size and location of tumour(s), laterality of disease, whether the disease is hereditary, risk for metastasis and SPTs, systemic status and the age of the patients.[2,3,13,35]

The treatment modalities currently available for retinoblastoma include enucleation, EBRT, brachytherapy, photocoagulation, cryotherapy, chemotherapy, thermotherapy and chemothermotherapy. Combinations of treatment may be required to achieve tumour control. An overview of treatment modalities including indication and technique used is provided in Appendix 2.

Historically, enucleation was the standard treatment used for cases of unilateral retinoblastoma. In cases of bilateral retinoblastoma, the eye with the most advanced tumour was commonly enucleated and the contralateral eye was given EBRT in an attempt to salvage the less affected eye. However, EBRT may be associated with the risk of developing radiation-induced SPTs and other long-term complications, including cataract, dry eye and facial growth asymmetry. The aims of treatment are to ensure survival and preserve the eye and salvage useful vision. This has led to an increasing trend towards the use of focal conservative treatments and chemotherapy and a subsequent decrease in the use of radiotherapy and enucleation, where possible.[13]

For the treatment of small tumours use of focal therapy such as cryotherapy, photocoagulation or

thermotherapy may be sufficient to control the tumour.[35,36] Chemotherapy can be used alone, or to reduce the size of the tumour to make it accessible to be treated with focal therapy or brachytherapy (chemoreduction). This is frequently used for the treatment of medium-sized intraocular tumours of RE group I–III. However, the use of chemotherapy for the treatment of RE group IV or V to avoid the use of EBRT or enucleation has varying levels of success.[37] Although it has been proposed that the addition of high-dose cyclosporine may be associated with improved tumour control in patients with more advanced intraocular retinoblastoma,[4] enucleation remains the treatment of choice for advanced cases of intraocular retinoblastoma. Adjuvant therapy following enuclation may be required if there is a high risk of metastatic disease.[13,38]

Chemoprophylaxis may be given to patients at high risk of developing extraocular retinoblastoma. Intensive chemotherapy (with or without orbital radiation) has been used to treat patients with extraocular and trilateral retinoblastoma, with varying levels of success.[37] The addition of autologous stem-cell rescue (ASCR) to chemotherapy has also been used to treat patients with metastatic disease.[35,39]

Follow-up

After the initial management of retinoblastoma, frequent follow-up investigations are recommended to allow for the timely detection of recurrent tumours, SPTs, metastatic disease or long-term complications. The frequency and timing of these investigations may vary according to the age and extent of disease at diagnosis, the laterality of the tumour, whether the tumour is hereditary and the type of treatment given.[4] Early recognition of risk factors for metastatic disease or long-term complications may further improve survival in patients with retinoblastoma.[27,28] Genetic counselling is regarded as an important aspect in the management of retinoblastoma.[3]

Chapter 3
Methods

Search strategy

The following databases were searched from their inception to April 2004 for studies published in any language: MEDLINE, MEDLINE In Process, EMBASE, Science Citation Index, BIOSIS, Pascal, LILACS and Cochrane Central Register of Controlled Trials (CENTRAL).

Unpublished research, ongoing trials and grey literature were searched for using the following resources: National Research Register (NRR), Current Controlled Trials, National Cancer Institute (NCI) Clinical Trials PDQ, International Cancer Research Portfolio (ICRP), System for Information on Grey Literature in Europe (SIGLE), NTIS, Greylit Network, Dissertation Abstracts, Inside Conferences.

Internet resources were searched using the Internet search engines OMNI and Google.

Attempts to identify further studies were made by contacting clinical experts and examining the bibliographies of all included articles.

Full details of the search strategies are given in Appendix 3.

Inclusion and exclusion criteria

Two reviewers independently assessed the titles, and where available, abstracts of all articles retrieved from the literature search. Full paper publications were obtained, where possible, for titles considered potentially relevant by either reviewer. Two reviewers independently assessed the eligibility of full-paper publications according to the criteria outlined below. Disagreements were resolved by discussion with reference to the original paper and, if necessary, a third reviewer was involved.

Participants

Studies of participants diagnosed with retinoblastoma at the age of 18 years or under were eligible for inclusion. Studies of adults were only included where childhood retinoblastoma was followed up into adulthood. Studies of mixed diagnoses were included if outcomes were reported separately for children with retinoblastoma.

Interventions

Any intervention or combinations of interventions given for the treatment of retinoblastoma were eligible for inclusion.

Outcomes

Studies reporting any clinical outcome were eligible for inclusion. The outcomes of interest included survival, progression-free survival, tumour response, preservation of the eye, visual acuity, disease remission and adverse effects.

Study design

Systematic reviews, randomised controlled trials (RCTs) and controlled trials were eligible for inclusion. However, it was not anticipated that many studies of these designs would be available. The scoping review[1] identified no RCTs, four systematic reviews and 24 potential non-randomised controlled trials. Study design classification in the scoping review was primarily based on information provided in the abstracts. Review of the full papers for this systematic review highlighted that many of these studies were retrospective cohort studies rather than controlled trials. Therefore, the decision was made that, where information from controlled trials was not available, cohort studies were eligible for inclusion provided that data from a comparison group were reported. Case series and case reports were excluded from the review owing to the high potential for bias in these study designs. Case–control studies (except where nested as part of a cohort study) and economic evaluations were also excluded.

Based on these inclusion criteria, it was confirmed that no controlled trials were available for inclusion in the review. Many of the remaining studies did not strictly fit common definitions of a cohort study, which can be variable. Therefore, at this stage, the inclusion criteria on study design were refined to include any studies in which a clear comparison between treatment groups appeared to be the objective from the outset of the study or, where this was not apparent, a clear

comparison had been made between groups in the results section and was not just one of many subgroup analyses. Initially, the intention was to include only prospective studies, but only three were found, all on chemotherapy; therefore, both prospective and retrospective studies with clear treatment comparison groups were eligible for inclusion.

Data extraction strategy

Data on study details, intervention(s), participants and outcomes were extracted for each individual study by one reviewer and checked for accuracy by a second. Disagreements were resolved by consensus, or with reference to a third reviewer if necessary. Where duplicate publications of the same study were identified, data were extracted and reported as a single study, making reference to the duplicate publications. The authors of publications were contacted, where possible. Where possible, the reviewers attempted to extract the most recent and/or comprehensive data for each study, which sometimes involved combining data from more than one publication. Studies of childhood retinoblastoma vary in the level of analysis used. Some base their analysis on number of eyes treated and others on number of children treated. Data were extracted based on the level of analysis used in each individual paper.

Quality assessment strategy

The quality of each individual study was assessed by one reviewer and checked for agreement by a second. Disagreements were resolved by consensus, or with reference to a third reviewer if necessary.

A recent review of potential tools for the quality assessment of non-randomised studies concluded that overall, the tools available are poorly developed with little consideration of the principles of scale development.[40] The six tools identified in the review as potentially useful for systematic reviews were considered for use in the current review. However, no one instrument covered the key issues that were considered important for the studies included in this review, combined with good usability. A list of quality criteria was therefore developed based on the review of quality assessment tools[40] and Centre for Reviews and Dissemination (CRD) Report No. 4[41] paying particular attention to how allocation occurred, any attempt to balance groups by design, identification of prognostic variables and case-mix adjustment (see Appendix 4).

Data synthesis

A mapping of the types of treatment on which effectiveness data were available is presented, as well as an overview of the quality of evidence available.

Extracted data for individual studies were summarised in structured tables and as a narrative. The quality assessment checklist for each individual study is presented in Appendix 5 and summarised within the text of the report. Full data extraction tables are contained in Appendix 6. The data on the effectiveness of treatment interventions were discussed with reference to the possible impact of study quality. Where possible, studies assessing common interventions were grouped together, with prospective and retrospective studies grouped separately. Owing to the diversity of studies in terms of interventions and comparators, patient population and outcomes assessed, statistical pooling was not performed.

Chapter 4
Results

Study selection

In total, 3114 titles and, where available, abstracts were identified and screened for eligibility. Seven-hundred and sixty full-paper copies of articles were retrieved and examined in further detail for inclusion in the review (*Figure 1*). It was not possible to retrieve full-paper copies or obtain further information on 12 articles identified.[42–53]

Excluded studies

Of the 760 articles examined in further detail, 665 were excluded from the review (*Figure 1*). A list of these studies, with reasons for exclusion, is available from the authors on request. Sixteen articles are awaiting translation.[54–69] The author(s) of two articles were contacted and further information is still awaited to determine the eligibility of their studies.[70,71]

Seventy-seven articles met the inclusion criteria for the initial screening process. Thirty-three of the studies were then excluded according to the revised inclusion criteria.[33,72–103] Closer assessment of the remaining articles excluded one further study owing to no actual data being presented for each treatment outcome[104] and one study owing to outcomes not being reported separately for each treatment group.[105]

Included studies

Forty-two articles met the inclusion criteria, reporting data on what appeared to be 31 individual studies. One of the included studies was obtained through contact with a clinical expert;[106] one study was identified through searching reference lists.[107] More than one paper has been published in relation to some cohorts of patients. These papers have been grouped and classified as one study, with data extracted from the most informative or most recent paper. Related papers, which provided additional information, are noted in the relevant extraction table in Appendix 6. Most studies had more than one intervention arm.

Overview of research evidence available

Study design

All of the studies, except for one, that were identified for inclusion in the review were comparative studies of observational design. One controlled trial was identified in which some of the participants were randomised to treatment.[107] The majority of the included studies were of a retrospective cohort design[5,38,106,108–131] and four were prospective cohorts studies.[107,132–134]

Treatment comparisons

Radiotherapy was a comparator in 21 studies, chemotherapy was a comparator in 13 studies, radiotherapy combined with chemotherapy was a comparator in four studies, with radiotherapy and/or chemotherapy a comparator in one study, enucleation was a comparator in six studies, and focal/local treatments were a comparator in five studies (*Table 1*). The four prospective studies all evaluated chemotherapy treatment. Two compared chemotherapy with no chemotherapy[107,132] and the other two studies compared two different chemotherapy regimens.[133,134]

Participants

The number of participants ranged from 21[110] to 1604.[5] In one study of chemotherapy, the patients had extraocular retinoblastoma.[130] The remaining studies were of patients with intraocular retinoblastoma or the type of retinoblastoma was not explicitly stated. Three studies explicitly stated that the participants had newly diagnosed retinoblastoma[130,131,133] and one study explicitly stated previous treatments that had been received.[38] However, the remaining studies were unclear as to whether patients had received previous treatments, although some specific previous treatments were excluded in individual studies. In the majority of studies, patients were treated in a single centre,[38,108–114,116,118,120,124,127,128,130–134] and in the remaining studies patients were from two or more centres or from a registry,[5,107,115,117,119,121–123,126,129] or it was unclear.[106,125] Four of the studies were of

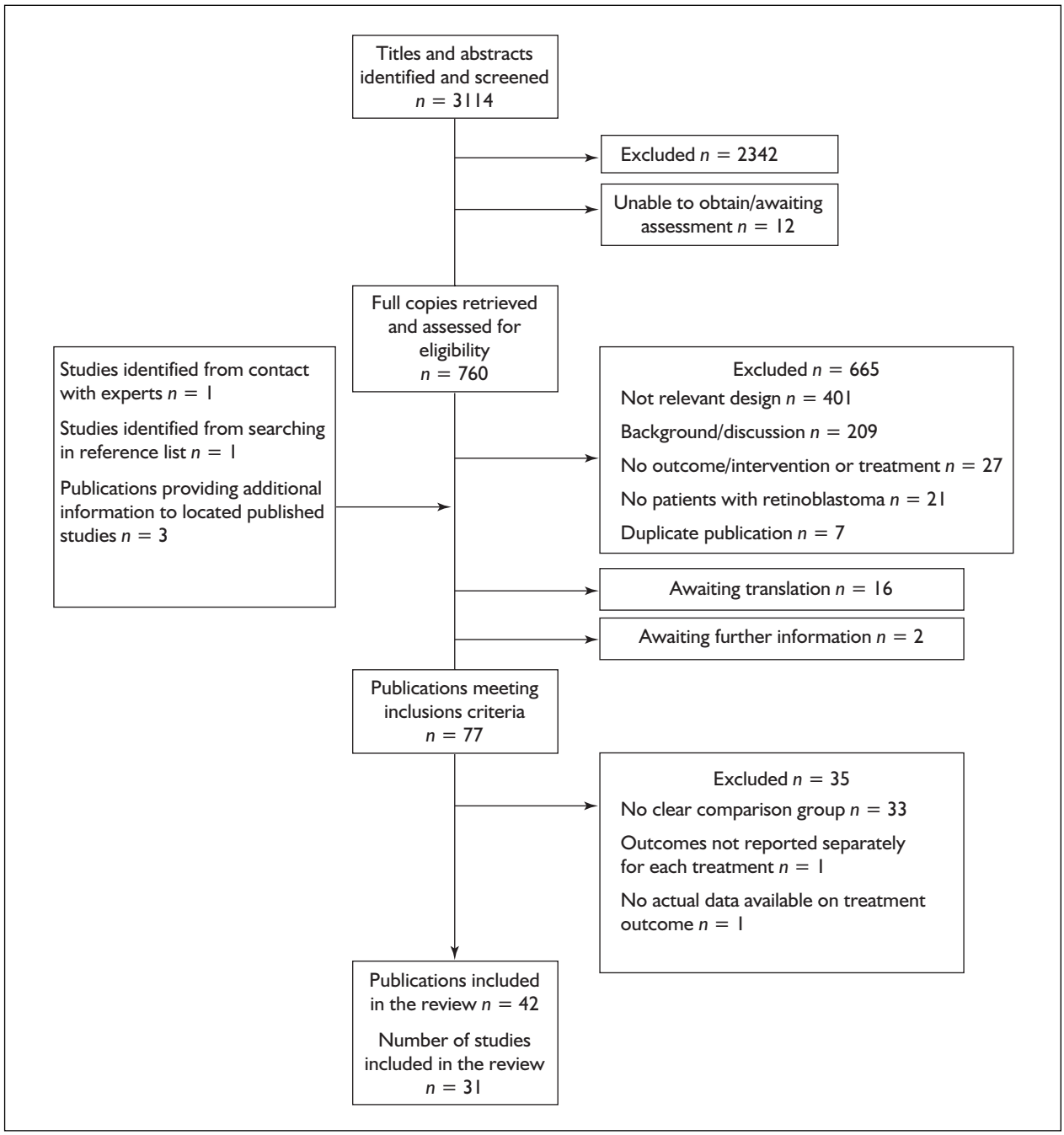

FIGURE 1 *Summary of study selection, retrieval and inclusion*

patients treated in the UK,[106,116,124,126] in 18 studies they were treated in the USA,[5,38,107,109–111,113–115,119,121–123,128,129,131,133,134] in six they were treated in a European country other than the UK[108,112,117,120,125,127] and in three in another non-European country.[118,130,132]

Studies were of hereditary or bilateral retinoblastoma patients only,[106,108,110,112,115,117,120,125,129] non-hereditary patients,[38] unilateral[107] and mixed types,[5,111,113,114,116,118,122,123,126–128,130–133] and five studies did not report this information.[109,119,121,124,134] Patients were most commonly classified at baseline for disease severity using the RE classification system.[38,106–109,111,113,121–124,127,128,132–134] Other systems used were the Children's Cancer Group (CCG) Classification for Extraocular Retinoblastoma[130] and Miller's classification.[118] In the remaining studies disease classification was not reported.[5,110,112,114–117,119,120,125,126,129,131]

TABLE 1 *Mapping of included studies by treatment comparison*

Radiotherapy	Chemotherapy	Radiotherapy combined with chemotherapy	Enucleation	Local treatments
21 studies	**13 studies**	**5 studies**	**7 studies**	**5 studies**
Versus no EBRT $n = 3$[5,115,117]	Versus no chemotherapy $n = 2$[131,132]	Versus chemotherapy $n = 3$[119,126,129]	Versus radiotherapy $n = 4$[114,118,120,125]	Brachytherapy versus radiotherapy $n = 2$[122,123]
Versus local therapy $n = 5$[108,110,112,122,123]	Versus EBRT $n = 3$[106,109,111]	Versus radiotherapy $n = 2$[126,127]	Versus chemotherapy with enucleation $n = 2$[38,107]	Photocoagulation versus radiotherapy $n = 1$[108]
Versus chemotherapy $n = 3$[106,109,111]	Chemotherapy with enucleation versus enucleation $n = 2$[38,107]	Versus enucleation $n = 1$[126]	Versus chemotherapy $n = 1$[126]	Other local treatments versus radiotherapy $n = 2$[110,112]
Versus enucleation $n = 4$[114,118,120,125]	Versus chemotherapy combined with radiotherapy $n = 3$[119,126,129]	Radiotherapy and/or chemotherapy versus no treatment $n = 1$[116]	Versus chemotherapy with radiotherapy $n = 1$[126]	
Versus radiotherapy combined with chemotherapy $n = 2$[126,127]	Different chemotherapy regimens $n = 3$[130,133,134]			
Different EBRT techniques $n = 4$[113,121,124,128]				
The number of studies does not add up to 30 as there was more than one treatment per study.				

Outcomes

The outcomes reported were diverse. The majority of studies were concerned with treatment effectiveness, with outcome measures including mortality, eye survival or salvage rate, disease-free survival, tumour recurrence, seed recurrence, eyes requiring additional treatment following primary therapy, metastases and tumour size. Four studies were concerned with the long-term risk of SPTs.[5,115,117,126] Medium- to long-term side effects on various aspects of growth were reported by a small number of studies.[114,119,120,125]

Quality assessment

Apart from one non-randomised controlled trial, all of the included studies were of observational design and shared the weaknesses of that study design in comparison with RCTs for assessment of treatment effects. None of the studies had randomised allocation with adequate allocation concealment and none had blinding of clinicians, participants or outcome assessors.

Over half of the studies did not describe how patients were assigned to treatment interventions.[5,106,108–110,112,114–120,122,125,126,132] Of those studies that did describe allocation of treatment, in some, patients were allocated to treatment on the basis of disease severity, with some information provided on indications for treatment.[111,113,123,127,129] In some studies treatment received depended on the period during which treatment was required, as there had been a change in the treatment protocol over time,[124,128,130,133,134] or on which clinic provided the treatment,[130] or generally it depended on the treatment protocol in use.[38,131] In the controlled trial some of the patients were randomly allocated to treatment group and some were not.[107] None of the observational studies balanced treatment groups by design, except for a study that carried out a nested case–control study based on the cohort.[5] Relevant prognostic variables were identified in 21 studies[5,106–109,111,113,116,118,121–124,127,128,130–134] This was generally RE classification or whether patients had bilateral or unilateral retinoblastoma. It was unclear, or not reported, whether treatment groups were comparable at baseline in 22 studies,[5,106,107,109,110,112–120,122,124–127,129,132,133] in five studies there was evidence that they were not comparable[38,108,123,131,135] and in four studies the groups were comparable on the factors assessed.[121,128,130,134] Four studies evaluated the effect of potential prognostic variables in statistical analyses and the remaining studies did not or it was unclear. However, some of these

remaining studies did report outcomes by RE classification.

In the majority of studies the number of patients lost to follow-up in individual treatment groups was unclear or not reported or, as the studies were retrospective, they included only patients on whom follow-up information was available.[38,106,109–116,119,120,122–132,134] In four studies the information was only reported for both treatment groups combined[5,117,118,130] and in three studies the information was available for both treatment groups.[107,108,133]

Thirteen studies reported the mean or median length of follow-up and range for both treatment groups;[38,106,107,111,115,117,119,121–124,128,131] eight did not do so or it was unclear;[108–110,118,120,126,127,132] ten reported this information for only both treatment groups combined.[5,112–114,116,125,129,130,133,134] The analyses were adjusted for different lengths of follow-up in ten studies, primarily through the use of Kaplan–Meier analysis.[5,38,112,115,117,121,125,126,128,130] Length of follow-up was assessed as long enough for the outcomes of interest to occur in 20 of the studies.[5,38,106–108,111–117,119–121,124,126–128,130] Treatment was rated as clearly specified in twelve studies[38,107,110,113,119–122,125,128,130,134] and criteria for measuring outcomes as clearly defined in 15 studies.[5,38,108,110–112,114,117,119,121,125,128,130,131,134]

In the synthesis four key criteria are discussed in relation to individual studies as these were considered central to the validity of observational studies: assignment to treatment group, identification of relevant prognostic variables, treatment group comparability at baseline and consideration of confounding variables in the statistical analysis. A fifth key criterion was whether groups were balanced by design. However, as none of the studies met this criterion, it was not helpful in distinguishing between studies.

EBRT techniques

Four retrospective studies compared EBRT techniques.[113,121,124,128] *Table 2* summarises the main study characteristics.

Study characteristics

Intervention

Two studies compared a lens-sparing technique with whole-eye EBRT[113,124] and two compared different lens-sparing techniques.[121,128] Foote and colleagues[113] investigated EBRT using a single, shaped, lateral temporal field by using a beam-splitting block positioned in the anterior aspect of the field at the central axis, with or without posterior angulation of the beam to spare the anterior segment in comparison with an anterior shaped field with no lens shield. This study has been more recently updated in an abstract.[136] The anterior lens-sparing technique used by Hungerford and colleagues,[124] in comparison with a whole-eye approach, was a modification of the Schipper technique. It is unclear how similar the techniques used in the two studies were.

Two studies investigated a modified lateral beam technique, one in comparison with an anterior lens-sparing approach[128] and one in comparison with a relative lens-sparing approach.[121] In one of the studies some children received chemotherapy or local therapy before radiation therapy.[113] In the remaining studies adjunctive treatment did not appear to be administered. The most recent treatment period for patients was 1989–1996.[121] The least recent period when a group received treatment was 1970–1985.[124]

Patients

The number of study participants ranged from 22 to 155. In one study the disease severity of the included eyes ranged from RE group I to group III.[124] The remaining studies included children with eyes from all five RE stages. Only one of the studies provided further information on baseline tumour characteristics such as vitreous seeding and retinal detachment. Two studies reported age at diagnosis: median 4.6 months (range 0.5–39.2 months)[113] and median 0.6 years (range 0.02–5 years).[121]

Outcomes

There was some variation between the studies in the outcomes reported. The summary of results below focuses on the outcomes common to all four studies: ocular survival, control of disease with radiotherapy alone and development of cataracts. Other outcomes are listed in *Table 2*, with results available in Appendix 6.

Study quality

The four studies were similar on some aspects of quality. All of the studies described the methods by which patients were assigned to the different treatment groups. Broadly, patients were allocated to type of EBRT based on the particular protocol used at the clinic where they were treated. In three studies, the type of EBRT received by patients was determined by the year in which they were treated, as the therapy used changed over time.[113,124,128] In

TABLE 2 *Summary of studies comparing EBRT techniques*

Study details	Techniques compared	Patients	Outcomes
Foote *et al.*, 1989;[113] USA **Treatment period** Both techniques were used from 1977 to 1987, with the whole-eye approach the most common approach later in the period	**Treatment 1** Lateral field with anterior segment-sparing techniques **Treatment 2** Anterior approach without a lens shield 39–51 Gy in 1.8–3.0-Gy fractions[a]	**Treatment 1** 10 participants (14 eyes) RE group I–III *n* = 10; group IV–V *n* = 8 **Treatment 2** 12 participants (16 eyes) RE group I–III *n* = 8; group IV–V *n* = 8	• Number of eyes given salvage therapy • Patient survival • Number of eyes developing cataract **Length of follow-up** Median 71.6 months (for both treatments combined)

Blach *et al.*, 1996;[128] USA
Treatment period
Treatment 1
1979–1984
Treatment 2
1984–1991
	Treatment 1
	Anterior lens-sparing technique
	38.5–50 Gy in 2.5-Gy fractions
	Treatment 2
	Modified lateral beam technique
	42–46 Gy in 2-Gy fractions
		Treatment 1[b]
		67 eyes
		RE
		group I *n* = 16;
		group II *n* = 10;
		group III *n* = 9;
		group IV *n* = 5;
		group V *n* = 27
		Treatment 2
		113 eyes
		RE
		group I *n* = 25;
		group II *n* = 22;
		group III *n* = 13;
		group IV *n* = 8;
		group V *n* = 45
		Total 123 participants
		104 bilateral; 19 unilateral
			• Freedom from relapse (no additional treatment required)
			• Eye survival (enucleation not required)
			• Development of cataracts
			• Cause-specific and overall survival
			Length of follow-up
			Treatment 1
			Mean 101 months
			(range 13–159 months)
			Treatment 2
			Mean 52 months
			(range 4–108 months)

Hungerford *et al.*, 1997;[124] UK
Treatment period
Treatment 1
1970–1985
Treatment 2
1986–1992
	Treatment 1
	Whole-eye EBRT
	35 Gy in nine or ten fractions to 40 Gy in 20 fractions
	Treatment 2
	Lens sparing
	40 Gy in 20 equal fractions
		Treatment 1
		102 participants (139 eyes)
		RE
		group I *n* = 16;
		group II *n* = 55;
		group III *n* = 68
		Treatment 2
		53 participants (62 eyes)
		RE
		group I *n* = 18;
		group II *n* = 33,
		group III *n* = 11
			• Tumour control (enucleation not required)
			• Number of eyes with new anterior tumours
			• Development of cataracts
			Length of follow-up
			Treatment 1
			Median 9 years
			(range 2–17 years)
			Treatment 2
			Median 3 years (range 1–7 years)

continued

TABLE 2 *Summary of studies comparing EBRT techniques (cont'd)*

Study details	Techniques compared	Patients	Outcomes
Scott *et al.*, 1999;[121] USA **Treatment period** 1989–1996	**Treatment 1** Relative lens sparing Mean dose = 43.5 (SD 3.9) at 1.8 Gy per fraction Median = 45 (range 36–49) **Treatment 2** Modified lateral beam Mean dose = 47.5 (SD 2.6) at 1.8 Gy per fraction Median 48 (range 44–54)	**Treatment 1** 18 participants (26 eyes) RE group I $n = 3$; group II $n = 2$; group III $n = 5$; group IV $n = 5$; group V $n = 11$ **Treatment 2** 24 participants (32 eyes) RE group I $n = 4$; group II $n = 5$; group III $n = 3$; group IV $n = 7$; group V $n = 13$	• Eye conservation rate • Tumour control (salvage therapy not required) • Development of cataracts • Midfacial hypoplasia • Other adverse events **Length of follow-up** *Treatment 1* Mean 40.3 months (SD 20.8) Median 39 months (range 5–74) *Treatment 2* Mean 36 months (SD 18.3) Median 36 months (range 7–72 months)

[a] For both treatments combined.
[b] The authors state that the two treatment groups were balanced in relation to RE classification, number of unilateral cases, initial age at diagnosis, administration of chemotherapy and family history of retinoblastoma (data reported for RE classification only).

two of these studies there was a clear time demarcation between the two treatments.[124,128] In the remaining study both treatments were used over the study period, with one of the treatments being more commonly used recently.[113] All of these studies are susceptible to factors that may introduce bias, such as changes in other aspects of care and diagnosis having a confounding effect with treatment. The most recent study compared patients from two clinics, each of which exclusively used relative lens-sparing or modified lateral beam technique;[121] in this case, although the period is the same, it is still unclear whether other important aspects of care may have varied between the two clinics. All of the studies reported the RE classification of the treated eyes. This was the only potential confounding variable considered in the statistical analyses: two studies reported some of the outcome measures by baseline RE classification[124,128] one study partly did so.[121] Two of the studies reported that the two treatment groups were comparable at baseline and also adjusted for different lengths of follow-up using Kaplan–Meier survival curves.[121,128]

Results

Whole eye versus lens sparing

In the update of the earliest included study, 50% ($n = 8$) of eyes treated with a whole-eye approach required additional treatment, compared with 71% ($n = 10$) with the lens-sparing approach.[113] The update did not report ocular survival, although the original publication did: overall ocular survival (eye survival after EBRT plus salvage therapy where necessary) was 81.8% ($n = 9$) and 78.6% ($n = 11$), respectively.[113] The other study investigating these two techniques reported that 85% of eyes treated with whole-eye EBRT plus salvage therapy (where necessary) did not require enucleation, compared with 92% with the lens-sparing approach (plus salvage therapy where necessary), with no significant difference between the two groups ($p = 0.68$).[124] This more recent study also reported the number of eyes with new anterior tumours. The development of new tumours was significantly lower in patients treated with the whole-eye technique than with the lens-sparing approach (1.4% versus 19%, $p = 0.001$), although significantly fewer patients treated with lens-sparing EBRT developed cataracts in the retained eyes (0% versus 100%, $n = 118$, $p < 0.0001$). Similarly, the earlier study reported fewer patients developing cataracts in the group receiving lens-sparing compared with whole-eye EBRT (29% versus 63%).[113]

Conclusions

The two studies are broadly in agreement. Lens-sparing EBRT alone was associated with a higher rate of relapse than whole-eye EBRT alone. In terms of ocular survival, lens-sparing EBRT in conjunction with salvage treatment was similar to

whole-eye EBRT in conjunction with salvage treatment, with a lower risk of cataract development with the lens-sparing treatment. However, these findings cannot be regarded as robust given the limitations of the study design used and, in particular, the use of historical controls.

Comparison of lens-sparing techniques

There was no significant difference in eye survival, defined as no enucleation required, between modified lateral beam and anterior lens-sparing technique at 5 and 8 years,[128] or between modified lateral beam and relative lens-sparing technique at 24-month follow-up.[121] The modified lateral beam technique was less successful for tumour control without the need for salvage therapy than the relative lens-sparing technique.[121] However, in the other study, it was more effective than the anterior lens-sparing technique.[128] Both studies reported no significant difference between treatment groups in the development of cataracts: 22% across both treatment groups in one study,[128] and in the other study 17% for the relative lens-sparing group and 37% for the modified lateral beam group.[121]

Conclusions

Given the limitations of the observational design used by these studies and the potential for bias owing to the way in which patients were allocated, it is not appropriate to make indirect comparisons between the two lens-sparing techniques. In one study there was a considerably shorter mean length of follow-up for the modified lateral beam group compared with the anterior lens-sparing group.[128] Although the two groups in the study comparing lateral beam with relative lens-sparing technique[121] had a similar follow-up period, this was shorter than in the other study.

Radiotherapy compared with no radiotherapy

Three retrospective studies compared radiotherapy with no radiotherapy.[5,115,117] The patient series reported by Wong and colleagues[5] was also reported in other publications, some of which provide additional or more recent data (Kleinerman RA *et al*., Gene environment interactions in a cohort of irradiated retinoblastoma patients: personal communication, 2004; Abramson and colleagues[137,138]). These studies were not concerned with the efficacy of treatment. They investigated the relationship between treatment and SPTs as a long-term adverse effect of treatment.

Study characteristics

Intervention

Table 3 summarises the main characteristics of the studies. All three studies investigated EBRT, although the EBRT technique was not reported in one study.[115] In one study all patients from 1971 were treated with a 6 or 8-MV photon beam in a 20 × 26-mm D-shaped field (Schipper technique), although information was not available on the techniques used before this.[117] One EBRT group received treatment at under 12 months old and one at over 12 months old. Some patients in both EBRT groups also received chemotherapy. In the other study a range of different forms of EBRT was used over the treatment period.[5] Before 1960 the majority of patients received orthovoltage radiation. Since then nearly all patients received cobalt-60 (^{60}Co) teletherapy or betatron (22 MV) or other megavoltage (mostly 6 MV) machines. The updated patient series received an average dose of 48 Gy (range 15–115 Gy) in 15 fractions (from Kleinerman RA: personal communication, 2004). The treatment received by the non-radiotherapy groups was not specified in any of the studies.

Patients

The patient cohorts were identified from hospital records in Boston and New York, with patients who had survived for 1 year or more after diagnosis included;[5] from the records of patients who had had an enucleated eye sent to the Registry of Ophthalmic Pathology (ROP) at the Armed Forces Institute of Pathology;[115] and from a national register (Dutch Retinoblastoma Register).[117] Two studies did not report patient age at diagnosis.[115,117] In the third study the median age at diagnosis for hereditary patients was 10 months and for non-hereditary patients was 23 months, although the age of patients by treatment group was not reported.[5] This study included both hereditary and non-hereditary patients.[5]

Outcome

All three studies were concerned with the development of SPTs. The outcomes reported in one study were the number of tumours inside and outside the field of radiation and the 10-, 20- and 30-year incidence of SPTs.[115] Incidence of SPTs was calculated with and without pineoblastoma. One study reported the number of SPTs and the cumulative incidence of SPTs at the age of 25 years inside and outside the field of radiation.[117] SPTs were defined according to the Warren and Gates criteria, that is, each of the tumours must present a definite picture of malignancy, each tumour must be distinct and the

TABLE 3 *Summary of studies comparing radiotherapy with no radiotherapy*

Study details	Intervention	Patients	Outcomes
Roarty *et al.*, 1988;[115] USA **Treatment period** 1922–1973	**Treatment 1** EBRT **Treatment 2** No radiotherapy	**Treatment 1** 137 participants (274 eyes) **Treatment 2** 78 participants (156 eyes) All bilateral disease	• Development of second primary tumours **Length of follow-up** Median 7.2 years (range 0–49.1 years)
Wong *et al.*, 1997;[5] USA **Treatment period** 1914–1984	**Treatment 1** EBRT **Treatment 2** No radiotherapy	**Treatment 1** 962 participants Hereditary $n = 848$; non-hereditary $n = 114$ **Treatment 2** 642 participants Hereditary[a] $n = 113$; non-hereditary $n = 529$	• Development of second primary tumours **Length of follow-up** Median 20 years
Moll *et al.*, 2001;[117] The Netherlands **Treatment period** Patients were born between 1945 and 1997	**Treatment 1** EBRT before 12 months old **Treatment 2** EBRT after 12 months old 45 Gy in 15 fractions, three fractions per week for both EBRT groups (after 1971) **Treatment 3** No radiotherapy	**Treatment 1** 128 participants **Treatment 2** 55 participants **Treatment 3** 80 participants All hereditary[b] retinoblastoma	• Development of second primary tumours **Length of follow-up** Mean 20 years (median 18 years, range 1 month to 48 years)

[a] Defined as hereditary if bilateral tumour or unilateral tumour with a family history of retinoblastoma.
[b] Defined as hereditary if patients had bilateral retinoblastoma, a positive family history or a defect in the retinoblastoma gene found in DNA analysis.

possibility that an SPT is a metastatic lesion of the primary tumour must be excluded. Pineoblastoma was not defined as an SPT. Sensitivity analysis was carried out based on whether or not pineoblastoma was defined as an SPT inside or outside the field of radiation.[117] In the third study the ratio of observed to expected SPTs and excess risk and cumulative incidence of SPTs at 50 years follow-up were reported.[5] Pineoblastoma was defined as an SPT. The follow-up of patients in the latter study has more recently been updated. Wong and colleagues[5] include patients up to December 1993 with a median length of follow-up of 20 years. Kleinerman and colleagues (personal communication, 2004)[137] include patients up to December 2000 with a mean length of follow-up of 25.2 years for hereditary retinoblastoma patients and 29.5 years for non-hereditary patients.

Nested case–control study

Within the cohort study, a nested case–control analysis was also performed.[5] Cases were patients identified from the cohort with sarcoma, based on data available from the first follow-up interview (1987–1988). One-hundred controls were randomly selected from the cohort on the basis of having bilateral retinoblastoma and being free of second cancer. Analysis was restricted to 83 cases (52 with bone sarcoma, 31 with soft-tissue sarcoma) whose radiation completeness of information ratings was fair or better. Information on radiation treatment was obtained from radiotherapy records. Absorbed dose was estimated by measurements and computer simulations. The average of the minimum and maximum calculated doses was used where there was uncertainty regarding treatment field or precise location of subsequent tumours. Risk of SPT was estimated for the following radiotherapy doses: 0–4.9, 5.0–9.9, 10.0–29.9, 30.0–59.9 and ≥ 60.0 Gy. Details of the analysis used can be found in the data extraction table (Appendix 6).

Quality

None of the studies reported how patients were allocated to treatment groups. It was unclear

whether the treatment groups in each of the studies were comparable at baseline. The study including hereditary and non-hereditary patients stratified outcome by this characteristic;[5] in the remaining studies all of the patients had bilateral[115] or hereditary disease.[117] No study considered additional potential confounding variables in the analysis.

Results

Roarty and colleagues[115] reported that 14.6% (n = 20) of patients who received radiotherapy developed SPTs, with 13 of these tumours inside the field of radiation, compared with 5.1% (n = 4) of patients in the group who did not receive radiotherapy. There was a significantly higher 30-year cumulative incidence of SPTs in patients who had received radiotherapy compared with those who had not [35.1% (SE 8.0) versus 5.8% (SE 4.4), p = 0.063].

Wong and colleagues[5] reported an excess risk of SPTs in hereditary patients in both the radiotherapy and non-radiotherapy groups, although there was a greater excess risk in those hereditary patients who had received radiotherapy compared with those who had not. The observed number of SPTs in the radiotherapy group was 180 for hereditary patients and three for non-hereditary patients; for the non-radiotherapy group ten SPTs were observed in hereditary patients and six in non-hereditary patients. In the radiotherapy group, the observed to expected ratio of SPTs was 36.7 [95% confidence interval (CI) 31.6 to 42.5] for hereditary patients and 2.7 (95% CI 0.6 to 7.9) for non-hereditary patients. In the group that did not receive radiotherapy, the ratio of observed to expected SPTs was 7.3 (95% CI 3.5 to 13.4) for hereditary patients and 1.3 (95% CI 0.5 to 2.9) for non-hereditary patients. In a more recent update of this study, the risk of SPTs in hereditary patients was increased almost seven-fold in those who did not receive radiotherapy. This risk was increased a further 3.1-fold (95% CI 2.0 to 5.3) with radiotherapy (Kleinerman RA *et al.,* personal communication, 2004).[137]

The nested case–control analysis showed a stepwise increase in risk (for bone and soft-tissue sarcomas) by radiation dose category (see data extraction table in Appendix 6 for further details).[5] In a related publication an analysis was carried out of a subset of 816 patients from the original cohort who had been treated in the New York Hospital and for whom age at initial radiation could be determined to the month. Kaplan–Meier survival curves were constructed with comparison made between patients treated with radiotherapy at less than 12 months of age, patients treated with radiotherapy at over 12 months of age and patients who received no radiotherapy. The authors concluded that the risk of tumours in the field of radiation was heavily dependent on the age at which EBRT is given and may be acceptably small to the patient after the age of 12 months.[137]

Moll and colleagues[117] reported 24 SPTs (patients with multiple SPTs were counted as one case) in the group receiving EBRT at less than 12 months, with ten inside the field of radiation; seven tumours in patients receiving EBRT at over 12 months, with four inside the field of radiation; and three tumours in the no-radiotherapy group. There was a higher overall cumulative incidence of SPTs in patients receiving EBRT at under 12 months old (22%, 95% CI 13 to 34%) compared with patients receiving EBRT at over 12 months (3%, 95% CI 0 to 14%) and patients receiving no radiotherapy (5%, 95% CI 1 to 16%). However, the cumulative incidence of SPTs was similar inside and outside the field of radiation for the group receiving EBRT at under 12 months, suggesting that radiotherapy may not be the cause. Sensitivity analysis showed that the results were affected by whether pineoblastoma was defined as an SPT and whether it was defined as inside or outside the field of radiation (see Appendix 6 for further details).

Conclusions

All three studies reported an increased risk of SPTs following EBRT compared with no radiotherapy. Radiotherapy treatment has changed over the long treatment periods of these studies and the differential effects of type of radiotherapy treatment are unclear. Variations between studies in the extent of the risk of SPTs may be explained by variations in population, treatments received, how outcomes were assessed and variations in other care given. These variations may also explain what appears to be contradictory evidence about the influence of age at which EBRT is administered. Although there was a reasonable length of follow-up in two studies, longer follow-up of patients into old age is required to establish the lifetime risk of SPTs in these patients.

EBRT compared with brachytherapy

Two retrospective studies investigated EBRT in comparison with brachytherapy.[122,123]

TABLE 4 *Summary of study investigating brachytherapy and EBRT*

Study details	Intervention	Patients	Outcomes
Amendola *et al.*, 1990;[122] USA **Treatment period** 1975–1988	**Treatment 1** Brachytherapy ^{60}Co, ^{125}I, ^{192}Ir, or ^{106}Ru was used 40 Gy to the midglobe and 100–120 Gy to the sclera **Treatment 2** EBRT 40–45 Gy (1.5–2 Gy daily) **Treatment 3** EBRT plus brachytherapy Initial EBRT was given elsewhere using various field arrangements. ^{60}Co and 4–6-MeV irradiation were used 35–45 Gy with daily fractions ranging from 1.5 to 3.5 Gy Salvage brachytherapy was given using ^{60}Co, ^{125}I or ^{192}Ir 40 Gy at the midglobe to 100 Gy at the sclera base where the plaque was attached	**Treatment 1** 24 participants (25 eyes) RE group Ia $n = 2$; group IIa $n = 15$; group IIIa $n = 4$; group IVA $n = 1$; group VA $n = 2$; group VB $n = 1$ **Treatment 2** 12 participants (13 eyes) RE group IIa $n = 2$; group IIb $n = 2$; group IIIa $n = 2$; group IVa $n = 2$; group VB $n = 3$ **Treatment 3** 27 participants (29 eyes) RE group IIIb $n = 1$; group V $n = 28$ 49 bilateral; 14 unilateral	• Treatment success (no evidence of disease) • Number of eyes developing cataracts • Number of eyes requiring additional treatment • Second tumours • Other adverse events **Length of follow-up** *Treatment 1* Median 38 months (range 5–115 months) *Treatment 2* Median 35 months (range 5–93 months) *Treatment 3* Median 49 months (range 6–126 months)

^{60}Co, cobalt-60; ^{125}I, iodine-125; ^{192}Ir, iridium-192; ^{106}Ru, ruthenium-106.

Study characteristics

Interventions

The main study characteristics are detailed in *Table 4*. One study compared EBRT alone with brachytherapy alone, and with EBRT with salvage brachytherapy.[122] This study includes some patients who were also included in the earlier study.[123] It is unclear whether these patients were from one treatment group only or from all treatment groups. The results are reported here for the more recent publication,[122] with the data extraction table for the earlier study contained in Appendix 6.

Patients

There were 63 patients, with an age range from birth to 5 years (mean 12.5 months). Patients from all five RE stages were included.[122]

Outcomes

Five outcomes were reported including adverse events. The main outcome, treatment success, was defined as no evidence of disease.[122]

Study quality

The description of treatment allocation was limited to describing clinical indications for treatment with brachytherapy, although it is probable that treatment was on the basis of clinical condition for all groups. The combined treatment group in this study received EBRT at another hospital. The RE classification of treated eyes and whether patients had bilateral disease was reported for each treatment group. However, outcomes were reported by RE classification for one outcome only. It was not stated whether patients were comparable at baseline. Based on the higher proportion of eyes with a group V RE classification, patients treated with EBRT plus brachytherapy had more severe disease. Different lengths of patient follow-up were not adjusted for in the analysis. The criteria for assessing some of the specific outcomes were unclear.

Results

A smaller proportion of the eyes receiving EBRT with salvage brachytherapy had no evidence of

disease compared with brachytherapy only and EBRT only (52%, $n = 15$, 88%, $n = 22$, and 85%, $n = 11$, respectively). For EBRT only, the abstract states that 77% of 13 eyes have no evidence of disease, but the text states that 11 eyes have no evidence of disease). In addition, more of the eyes receiving combination therapy required eventual enucleation (48%, $n = 14$) than the other two treatment groups (12%, $n = 3$, and 15%, $n = 2$ for brachytherapy and EBRT, respectively). The number of retained eyes developing cataracts was smallest in the group that received no EBRT (10%, 45% and 60% for brachytherapy, EBRT and combined treatment, respectively). Four patients in the combination therapy group developed second tumours; one developed dense lens opacification of the eye; one moderate optic nerve atrophy; three neovascular glaucoma and four vitreous haemorrhages, and there was one death.

Conclusions

The finding that EBRT in combination with brachytherapy is apparently less effective is not surprising given that all the patients except for one in this group had eyes classified at baseline as RE V. The median length of follow-up was also longer in this group. EBRT and brachytherapy appear to be equally effective, although there was a higher rate of cataracts in the former. However, this finding cannot be regarded as robust given the limitations of the study design and, in particular, treatment allocation.

Radiotherapy alone compared with radiotherapy in combination with triethylene melamine

One retrospective study compared radiotherapy alone with radiotherapy in combination with intra-arterial or intramuscular triethylene melamine (TEM).[109] TEM is no longer used as a treatment in retinoblastoma; therefore, the results are not discussed here, although they are available in Appendix 6.

Radiotherapy compared with local treatment

Three retrospective studies compared radiotherapy with local treatments.[108,110,112]

Study characteristics

Intervention

Table 5 summarises the main characteristics of the three studies. In one study, only patients who had received megavoltage EBRT were included.[112] The EBRT group in this study included a subgroup of patients who had been treated with a lateral canthus approach ($n = 73$) and a subgroup treated with a beam alignment technique adapted from Schipper's technique ($n = 54$). One study used a 4-MV linear accelerator using a lateral beam to deliver 80–85% of the dose and an anterior beam to deliver 15–25% of the dose.[110] The remaining study provided no details of the EBRT used.[108] In one study the comparison was with photocoagulation,[108] and in the other two studies the comparison group received photocoagulation, cryocoagulation or brachytherapy;[110,112] in one of these studies patients were not included if EBRT had been performed within 4 weeks of initiation of local therapy.[112] Cryotherapy using a triple-thaw technique, photocoagulation using a diode laser and brachytherapy using ^{125}I plaques were used in one study.[110] In the other study using multiple focal treatments, ^{106}Ru or ^{60}Co plaques were used for brachytherapy patients.[112] In one study, four patients in the local therapy group also received EBRT and four patients in the EBRT group also received chemotherapy.[110] In one study secondary or additional EBRT or secondary chemotherapy was used, although patients receiving these adjunctive treatments were classified as lost to follow-up from the beginning of the new course of treatment for new or recurrent tumours.[112]

Patients

The number of participants ranged from 21 to 200 and all patients were classified as having hereditary[110,112] or bilateral retinoblastoma.[108] One study excluded patients with RE stage V retinoblastoma,[110] in one study participants ranged from RE group I to V,[108] and in one study eyes with total retinal detachment, diffuse vitreous seeding or tumours larger than half of the retina were excluded.[112] In one study the mean age of participants in the EBRT group was 12.2 months and in the local treatment group was 6.7 months,[108] and in one study mean age was 6 months for the EBRT group and 11.3 months for the local therapy group.[110] This information was not reported for the third study.[112] Patients in all three studies were treated at single centres.

Outcomes

This group of studies focused on similar outcomes. All studies reported data on development of new and recurrent tumours, although the level of detail in relation to how the outcomes were defined varied between studies. There was also some variation in how the data on new and recurrent tumours were reported. One study reported the

TABLE 5 *Summary of studies comparing EBRT with local therapies*

Study details	Intervention	Patients	Outcomes
Messmer *et al.*, 1990;[112] Germany **Treatment period** *Treatment 1* 1960 onwards *Treatment 2* 1974–1988	**Treatment 1** Photocoagulation, cryocoagulation or brachytherapy 40 Gy in 70% of cases receiving brachytherapy **Treatment 2** EBRT Megavoltage therapy 40–50 Gy	**Treatment 1** An 'unselected subseries' of 77 patients (83 eyes) was used for the analysis **Treatment 2** 127 eyes All hereditary retinoblastoma	• Number of applications of local therapy to sterilise tumour • Development of new tumours • Development of recurrent tumours • Latency between initiation of therapy and detection of new tumour **Length of follow-up** Mean 7.1 years (median 5.8 years, range 0–23 years)
Hadjistilianou *et al.*, 1991;[108] Italy **Treatment period** 1960–1990	**Treatment 1** Light or photocoagulation **Treatment 2** EBRT	**Treatment 1** 7 participants (7 eyes) RE group I $n = 4$; group II $n = 3$ **Treatment 2** 16 participants (16 eyes) RE group I $n = 2$; group II $n = 4$; group III $n = 7$; group IV $n = 2$; group V $n = 1$ All bilateral retinoblastoma	• Development of new tumours • Development of recurrent tumours • Latency to development of new and recurrent tumours **Length of follow-up** Not stated
Merrill *et al.*, 1996;[110] USA **Treatment period** 1983–1993	**Treatment 1** EBRT 43.8 Gy with a mean dose per fraction of 1.84 Gy once daily for 5 days per week **Treatment 2** Cryotherapy, photocoagulation or brachytherapy	**Treatment 1** 12 participants (15 eyes) **Treatment 2** 9 participants (9 eyes) All hereditary retinoblastoma	• Development of new tumours • Development of recurrent tumours **Length of follow-up** Not stated

percentage of eyes,[112] one reported the number of new tumours and number of eyes affected,[108] and one reported the number of patients affected.[110] Two studies also reported the length of time to development of new tumours.[108,112]

Quality

None of the studies described the method of assignment of patients to treatment group and only one of the studies reported any information on a relevant prognostic variable (RE classification).[108] In the latter study the two treatment groups differed on RE classification at baseline, with the EBRT group having more serious disease. It was unclear whether the treatment groups in the other two studies were comparable at baseline.[110,112] Length of follow-up was reported in only one study, although the information was not reported separately for the two treatment groups.[112]

Results

Merrill and colleagues[110] reported no significant differences between EBRT and local treatment for new (7%, $n = 1$, and 11%, $n = 1$, respectively) and recurrent tumours (7%, $n = 1$, and 11%, $n = 1$, respectively). Here, 'new' means a tumour appearing at the distant site unrelated to any prior tumour, and 'recurrent' means regrowth of a tumour within or next to the scar of the regressed tumour.

The other two studies did not make statistical comparisons between treatment groups. In one of these studies a similar proportion of patients in both treatment groups developed new (20% and 27% for local treatment and EBRT, respectively) and recurrent tumours (26% and 28% for local and EBRT treatment, respectively).[112] Here 'new' means tumours that had no relationship to pre-existing tumours and were observed more than 4 weeks after the initiation of therapy, and 'recurrent' means tumours that developed from previously successfully treated areas (i.e. had been described as inactivated). In the other study the situation is less clear; 86% of eyes developed new tumours in the photocoagulation group and 19% in the EBRT group; 43% and 25%, respectively, developed recurrent tumours.[108] Here, 'new' means tumours not present at time of initial treatment, and 'recurrent' means tumour growth that originates, after successful treatment, at the margin or within the scar of the inactive, regressed tumour.

In one study the average number of applications of local therapy necessary to 'sterilise' (this is not defined in the paper) the tumour differed for type of local therapy: cryocoagulation (n = 27 tumours) average 1.6 applications, and photocoagulation (n = 69 tumours) average 2.6 applications, and plaque therapy (n = 10 tumours) average 1 application (p = 0.0039 cryocoagulation versus photocoagulation).[112] This study also found a shorter median time interval between initiation of therapy and detection of a new tumour in the local therapy group (p = 0.02). Additional subgroup analyses for this study are reported in the data extraction table (Appendix 6). The mean number of months to occurrence of new tumours was 7.6 months for the photocoagulation group and 9.5 months for the EBRT group; for recurrent tumours the mean length of time was 11 months for photocoagulation and 10.6 months for EBRT.

Conclusions

It is difficult to make meaningful comparisons between these studies as it is unclear how similar the patients are across the studies at baseline. From the limited information that is available there may be important differences; for example, one study specifically excluded RE group V patients and one did not. Although it is not explicitly stated, treatment allocation was probably on the basis of disease severity according to hospital protocol. However, the similarity of the treatment protocol between studies is unclear. The length of follow-up is also unclear in two of the studies.[108,110]

Chemotherapy compared with radiotherapy

Two retrospective studies compared radiotherapy with chemotherapy.[106,111]

Study characteristics

Intervention

One study did not specify the form of chemotherapy treatment used.[106] *Table 6* details the chemotherapy treatment used in the second study.[111] For the radiotherapy intervention one study used relative lens-sparing EBRT[111] and one used lens-sparing EBRT.[106] In one study there was no standard adjunctive therapy for either treatment group although, where necessary, salvage therapy was used.[106] In the second study all the patients in the chemotherapy group received transpupillary diode laser therapy and 50% of them received cryotherapy immediately before the chemotherapy cycles, and in the EBRT group two patients received no adjunctive treatment, one received transpupillary diode laser therapy, two received cryotherapy and three received diode laser or cryotherapy.[111]

Patients

One of the studies had a smaller sample size (n = 26)[111] than the other (n = 85).[106] Disease severity as assessed by RE classification varied between the two studies. One study included only patients with more advanced disease (group IV–Vb)[111] and in the other participants were from group I–III.[106] The age of participants by treatment group was reported in only one study: the mean age at diagnosis in the chemotherapy group was 9 months (SD 11) and in the EBRT group was 17 months (SD 15).[111]

Outcome

The two studies used different outcome measures. One reported on treatment success, defined as tumour control with primary treatment as well as tumour control with primary and salvage treatment.[106] Other key outcomes reported in this study are detailed in *Table 6*. Reduction in tumour volume was the main outcome of interest in the other study, reported as mean percentage of baseline volume.[111]

Study quality

Treatment allocation appeared to be on the basis of RE classification in one study: it was stated that group I–III patients at the clinic were initially treated with focal therapy, whereas group IV and V patients were treated initially with chemoreduction or EBRT.[111] However, it was unclear in this study

TABLE 6 *Summary of studies comparing radiotherapy with chemotherapy*

Study details	Intervention	Patients	Outcomes
Sussman *et al.*, 2003;[111] USA **Treatment period** 1991–2001	**Treatment 1** Chemotherapy using carboplatin, vicristine sulphate and etoposide phosphate with or without cyclosporine Administered every 3 weeks with a target of nine cycles (mean received seven) **Treatment 2** Relative lens-sparing EBRT 43.2–45.0 Gy delivered in a single daily fraction at 1.8 Gy for approximately 3 weeks	**Treatment 1** 18 participants RE group IV or V $n = 10$; group Vb $n = 8$ Hereditary $n = 8$; sporadic $n = 10$ **Treatment 2** 8 participants RE group IV or V $n = 3$; groupVb $n = 5$ All sporadic	• Reduction in tumour volume • Complications • Conserved globes • Mortality • Free of metastases **Length of follow-up** Mean 35 months (range 6–72 months) for both treatment groups
Hungerford, 2004;[106] UK[a] **Treatment period** Not stated	**Treatment 1** Systemic chemotherapy **Treatment 2** Lens-sparing EBRT	**Treatment 1** 39 participants (49 eyes) RE All group I–III **Treatment 2** 46 participants (61 eyes) RE All group I–III	• Tumour control with primary treatment • Tumour control with primary and salvage treatment • Number of salvage treatments • Overall success rate of salvage treatment • Reasons for failure of primary treatment **Length of follow-up** *Treatment 1* Median 36 months (range 12–73 months) *Treatment 2* Median 93 months (range 30–193 months)

[a] Data extraction from this study was based on slides from a conference presentation.

why patients were allocated to chemotherapy or EBRT. Information on treatment allocation was not reported in the other study.[106] Although the RE classification of participants was reported in both studies, neither study matched patients for this or any other potentially confounding variable or considered the effect of any potentially confounding variables in the statistical analysis. It was unclear in one study whether the intervention groups were comparable at baseline.[106] In the other study the mean age of patients in the chemotherapy group was younger than the EBRT group, and the EBRT group had no patients with hereditary retinoblastoma, whereas approximately half the patients in the chemotherapy group had hereditary retinoblastoma.[111]

Results

Sussman and colleagues[111] reported a statistically significant greater reduction in tumour volume in the chemotherapy treatment group compared with the relative lens-sparing EBRT group at 1 month [32% (SD 26) versus 88% (SD 32), $p = 0.004$)] and 2 months [19% (SD 15) versus 42% (SD 32), $p = 0.04$], but not at 12-month follow-up [9% (SD 17) versus 6% (SD 2), $p = 0.76$]. Significantly more patients in the EBRT group developed a cataract, although there were no other differences in treatment complications between the two treatment groups. At time of last follow-up, all patients in both groups were alive, had conserved globes and were free from metastases.

Hungerford[106] reported similar levels of tumour control for the chemotherapy and radiotherapy treatment groups after salvage therapy was administered, where necessary (94%, $n = 46$, for chemotherapy versus 96%, $n = 59$, for lens-sparing EBRT). With primary treatment only, a smaller proportion of eyes was classified as treatment successes in both groups (29%, $n = 14$, for chemotherapy versus 53% for EBRT). On average, 2.14 salvage treatments were required for the radiotherapy group and 2.94 for the chemotherapy group, with an overall success rate of salvage treatment of 93% ($n = 27$) and 91% ($n = 32$), respectively. These data are also reported by RE classification in the data extraction table (Appendix 6), although the number of patients in each RE group is unclear.

Conclusions

Because of differences in treatment, patients and outcomes measured, it is not possible to compare the findings of these two studies of radiotherapy versus chemotherapy. It is unclear whether differences between the two treatment groups in prognostic factors, in each study, may have influenced treatment outcomes. In one study, all the patients in the radiotherapy group had the sporadic form of disease and were older at diagnosis.[111] In addition, as outlined earlier, it is unclear why some patients were allocated to chemotherapy and others were not in this study. It is difficult to make definite conclusions from the second study at this stage as the information extracted is based on a conference presentation and full details of the study design are not available.[106]

Chemotherapy and radiotherapy combined

Four retrospective studies investigated radiotherapy and chemotherapy combined.[119,126,127,129]

Study characteristics

Intervention

The main study characteristics are reported in *Table 7*. One of the studies compared the combined treatment with chemotherapy alone,[129] one compared the combined treatment with radiotherapy alone,[127] one compared the combined treatment with chemotherapy alone, radiotherapy alone and enucleation,[126] and one compared the combined treatment with chemotherapy only or retinal radiotherapy with chemotherapy.[119] In one study both treatment groups received chemotherapy with vicristine and cyclophosphamide weekly for 1 year. In the earliest study, some patients in the chemotherapy and radiotherapy groups also underwent enucleation.[126] The patients in the enucleation-only group received no chemotherapy or radiotherapy. In the study comparing EBRT or brachytherapy with chemotherapy, no details were provided on the EBRT technique used.[127] *Table 7* provides details of the chemotherapy treatment used in this study. Additional treatment was provided 'if necessary'; however, it was unclear whether this referred to both treatment groups.[127] In the final study, patients were treated with focal therapy if chemotherapy resulted in a small enough tumour. Local treatments used were cryotherapy and photocoagulation; however, it was unclear how many patients received these treatments.[129]

Patients

The number of study participants ranged from 28 to 882. One study included exclusively patients with hereditary retinoblastoma[129] and one included hereditary and non-hereditary patients.[126] Two studies did not report type of retinoblastoma.[119,127] The mean age at diagnosis was different for the two studies reporting this information.[119,129] One reported a mean age of 6.4 months (range 0–29 months)[129] and the other a mean age of 24 months (range 1–56 months).[119] Both studies also reported age by treatment group. Patients were identified from a single hospital,[119,127] from two hospitals,[129] and in the study investigating SPTs, patients were identified through the National Cancer Registration Scheme and other registries, with only 3-year survivors included before 1962.[126]

Outcome

Diverse outcomes were reported: treatment success, although this was not clearly defined,[127] development of new tumours and number of eyes enucleated,[129] height[119] and the development of SPTs.[126] The latter study defined SPTs as all malignant neoplasms and all neoplasms of the brain, except for certain tumours of the pineal and suprasellar regions.

Study quality

Two studies did not specify how patients were allocated to treatment groups.[119,126] Treatment allocation appeared to be on the basis of disease or clinical condition in two studies.[127,129] In the earlier study it was stated that patients with RE group I–IV tumours were treated with EBRT or brachytherapy and group V tumours with chemotherapy and EBRT.[127] However, in the results reported for group I and II patients, some appear

TABLE 7 *Studies with chemotherapy combined with radiotherapy as an intervention*

Study details	Intervention	Patients	Outcomes
Draper *et al.*, 1986;[126] UK **Treatment period** 1950–1977	**Treatment 1** EBRT or brachytherapy EBRT dose 15–80 Gy Cobalt or radium plaques were used for brachytherapy **Treatment 2** Chemotherapy Cyclophosphamide with or without other drug treatments **Treatment 3** Chemotherapy and EBRT or brachytherapy As above **Treatment 4** Enucleation	**Treatment 1** 319 participants 241 genetic; 78 non-genetic **Treatment 2** 11 participants 3 genetic; 8 non-genetic **Treatment 3** 95 participants 73 genetic; 22 non-genetic **Treatment 4** 457 participants 67 genetic; 390 non-genetic	• Number of patients developing second neoplasm • Incidence of second neoplasms among genetic retinoblastoma patients **Length of follow-up** Interval since retinoblastoma to developing second tumours ranged from 31 to 220 months
Haye *et al.*, 1989;[127] France **Treatment time period** 1977–1981	**Treatment 1** Primary radiotherapy: either EBRT or cobalt plaque Dose not stated **Treatment 2** Primary chemotherapy: vincristine, actinomycin and cyclophosphamide Two courses, followed by a further six courses after EBRT Dose not stated	**Treatment 1** 33 participants RE group I $n = 17$; group II $n = 16$ Treatment 2 12 participants RE group I $n = 2$; group II $n = 10$	• Treatment success and failure **Length of follow-up** Minimum of 5 years, although exact length not stated
Pasqualini *et al.*, 1991;[119] Argentina and USA **Treatment period** Not stated	**Treatment 1** Chemotherapy and no radiotherapy or retinal radiotherapy only Mean 55 Gy (SD 16.9) **Treatment 2** Chemotherapy and cranial with or without orbital radiotherapy Orbital mean 29.3 Gy (SD 5.5); orbital mean 45.42 Gy (SD 11.52)	**Treatment 1** 10 participants **Treatment 2** 18 participants	• Height **Length of follow-up** Not explicitly stated, although mean age at follow-up was 125 and 128 months for the two treatment groups
Lee *et al.*, 2003;[129] USA **Treatment period** 1994–2000	**Treatment 1** Chemotherapy Systemic carboplatin **Treatment 2** Chemotherapy followed by EBRT or brachytherapy Systemic carboplatin; EBRT via a lateral lens-sparing portal (dose not stated); or brachytherapy using ^{125}I plaques	**Treatment 1** 13 participants (25 eyes) **Treatment 2** 21 participants (32 eyes) All participants had bilateral and hereditary retinoblastoma	• Development of new tumours • Development of new tumours according to age at treatment • Number of eyes enucleated **Length of follow-up** Mean 35.7 months (range 12–81 months)

to have received chemotherapy. In the final study, treatment response to initial chemotherapy determined whether or not patients received radiotherapy (EBRT or plaque therapy)[129] It was unclear whether the treatment groups were comparable at baseline on relevant prognostic factors in any of the four studies, although in one of the studies the enucleation treatment group and the chemotherapy treatment group had a smaller proportion of hereditary patients than the other two treatment groups.[126] Only very limited analyses were carried out taking into consideration potential confounding variables. A stratified analysis based on age at initial treatment was carried out by one study, but other potential confounding variables were not considered.[129] The study investigating SPTs carried out a separate analysis on patients with genetic retinoblastoma.[126]

Results

In the earliest study there was a higher proportion of patients classified as treatment successes in the radiotherapy group (88% of patients: 94% RE group I, 81% group II), compared with chemotherapy combined with radiotherapy (58%: 50% RE group I, 60% Group II) although the authors state that the difference was not statistically significant.[127] However, it is unclear why any of these patients received chemotherapy, given that only group V patients were generally allocated to chemotherapy treatment. Although the two treatment groups were similar for RE classification at baseline, it is unclear whether there were other differences between the two groups. In addition, the authors do not specify how they defined treatment success; therefore, it is unclear what the outcome actually means in this instance.

Draper and colleagues.[126] reported 16 SPTs (in 319 patients) in the radiotherapy group (EBRT or brachytherapy), one (in 11 patients) in the chemotherapy group; nine (in 95 patients) in the chemotherapy combined with radiotherapy treatment group, and four (in 457 patients) in the enucleation group. Twenty-six of the 30 cases of SPTs were in patients with the hereditary form of the disease; 12 of the 26 tumours in the hereditary group were outside the field of radiation and 17 were osteosarcomas. At 18 years the cumulative incidence of all SPTs in the hereditary patients was 8.4% for all sites, 6.6% inside the field of radiation (radiotherapy group), 3.0% outside the field of radiation for all treatments (including non-irradiated patients) and 2.2% for those patients who received no chemotherapy. To examine the effect of chemotherapy, only patients from 1962 onwards were included. Cumulative incidence rates of all SPTs were reported for patients treated with chemotherapy compared with patients given radiotherapy, patients not given radiotherapy, and patients receiving chemotherapy and radiotherapy (see Appendix 6 for further details). However, this analysis included only 65 at-risk patients in the chemotherapy group as a whole, with three at-risk patients in the chemotherapy-only group. This is too small a group of patients on which to base conclusions about chemotherapy and the incidence of SPTs. The impact of other possible confounding factors is also unclear.

Height retardation was greater in the orbital radiotherapy group in one study.[119] The height of patients was normalised by expressing it as a standard deviation score (SDS) in relation to the mean for age and gender (further details not reported). The height SDS was significantly ($p < 0.05$) lower in the group treated with cranial radiotherapy in combination with chemotherapy [height mean SDS –0.9 (SD 1.3)] compared with the group receiving no radiotherapy or retinal radiotherapy with chemotherapy [height mean SDS 0.02 (SD 1.2)].

Lee and colleagues[129] reported broadly similar proportions of eyes developing new tumours with chemotherapy-only treatment compared with chemotherapy followed by EBRT, although statistical comparisons were not made (56%, $n = 14$, versus 41%, $n = 13$). Using Kaplan–Meier analysis, the probability of an eye remaining tumour free was 69% in children treated after 6 months old and 40% in children who were treated before the age of 6 months ($p = 0.0182$), with a similar trend in both treatment groups. The number of eyes eventually enucleated was 16% following chemotherapy and 18.8% for chemotherapy combined with EBRT.

Conclusions

Given the diversity of patients, treatments received and outcomes assessed in this group of studies comparing chemotherapy with no chemotherapy, the results of each study need to be considered individually. None of the findings can be regarded as robust given the limitations of study design and, in particular, treatment allocation.

Chemotherapy compared with no chemotherapy

One partly prospective study[132] and one retrospective study compared chemotherapy with no chemotherapy.[131]

TABLE 8 *Summary of studies comparing chemotherapy with no chemotherapy*

Study details	Intervention	Patients	Outcomes
Akiyama *et al.*, 1989;[132] Japan **Treatment period** *Treatment 1* 1979–1985 *Treatment 2* 1980–1981	**Treatment 1** Chemotherapy Vincristine and cyclophosphamide alternating every 2 weeks for most patients **Treatment 2** No chemotherapy Treatments received not specified, although conservative treatments were administered	**Treatment 1** 14 participants (18 eyes) RE group Ia $n = 1$; group IIa $n = 1$; group IIb $n = 2$; group IIIb $n = 1$; group IVb $n = 1$; group Va $n = 8$; group Vb $n = 4$ Bilateral $n = 4$; unilateral $n = 10$ **Treatment 2** 37 participants (37 eyes) RE group Ia $n = 1$; group Ib $n = 2$; group IIa $n = 1$; IIIa $n = 1$; group IIIb $n = 2$; group IVb $n = 3$; group Va $n = 20$; group Vb $n = 7$ All unilateral retinoblastoma	• Survival **Length of follow-up** *Treatment 1* Not stated *Treatment 2* Not specified; at least 5 years
Shields *et al.*, 2001;[131] USA **Treatment period** 1995–1999	**Treatment 1** Chemoreduction therapy Vincristine sulphate, etoposide phosphate and carboplatin **Treatment 2** No chemoreduction therapy Treatments received included EBRT, brachytherapy, thermotherapy, laser photocoagulation and cryotherapy	**Treatment 1** 142 participants $n = 99$ patients with bilateral or familial retinoblastoma **Treatment 2** 72 participants $n = 18$ patients with bilateral or familial retinoblastoma	• Prevalence of trilateral retinoblastoma **Length of follow-up** *Treatment 1* Mean 34 months (median 6 months; range 0–67 months) *Treatment 2* Mean 30 months (median 31 months; range 5–58 months)

Study characteristics

Intervention

The main study characteristics are detailed in *Table 8*. The prospective study compared intravenous therapy of vincristine and cyclophosphamide with no chemotherapy.[132] Details of dose and number of chemotherapy treatments are available in Appendix 6. In the chemotherapy group, all patients with bilateral retinoblastoma also received xenon photocoagulation, cryosurgery and enucleation of the worse eye. Patients with unilateral retinoblastoma were enucleated initially. Treatments received by the comparison group were not specified, other than that patients did not receive chemotherapy.

The retrospective study compared neoadjuvant intravenous chemotherapy (chemoreduction) with no chemoreduction.[131] Patients in the chemoreduction group received a mean of five 28-day cycles (range 2–13 cycles). Details of drug dosage are detailed in the data extraction table (Appendix 6). These patients also received focal adjuvant therapy, but the focal therapies received were not specified. The comparison group received no chemotherapy. The therapy received by patients in this group was not specified, although the authors reported that treatment received included EBRT, brachytherapy, thermotherapy, laser photocoagulation and cryotherapy.

Patients

The 51 patients in the prospective study had eyes ranging from RE group I to group V.[132] Mean age at diagnosis was 21.9 months (range 2–54 months) for the chemotherapy group. This information was not reported for the comparison group. Patients in the chemotherapy group were treated at a single

centre. The patients in the comparison group were obtained from a national register.

The retrospective study included 214 patients with newly diagnosed retinoblastoma.[131] Patients with familial and sporadic retinoblastoma were included. Patients with bilateral and/or familial retinoblastoma were defined as being at risk of developing trilateral retinoblastoma. Mean age at diagnosis was 14 months (range 1–87 months) in the chemoreduction group and 24 months (range 1–110 months) in the comparison group. Patients were identified at a single hospital.

Outcome

The single outcome of survival was reported in the prospective study.[132] Prevalence of trilateral retinoblastoma was assessed in the retrospective study.[131] The expected number of patients developing trilateral retinoblastoma was derived from a meta-analysis[18] and the observed and expected number of cases were reported for all patients, at-risk patients and patients with unilateral sporadic retinoblastoma. All patients underwent annual or biannual routine MRI or computed tomography (CT) of the CNS until aged 4 or 5 years to ascertain the development of pineal tumour or other intracranial neuroblastic tumours.

Quality

Data on the chemotherapy treatment group were gathered prospectively, whereas the comparison group was retrospective. Patients from the chemotherapy group appeared to be allocated to that particular treatment based on hospital treatment protocol. RE classification at baseline was reported. The influence of potential confounding variables was not considered in the analysis; however, given that there was only one event (one patient did not survive), further analysis would not have been possible.

The medical records of newly diagnosed patients with retinoblastoma were reviewed over a 54-month period in the retrospective study.[131] Treatment allocation was based on the hospital treatment protocol: children with intraocular retinoblastoma who would otherwise require treatment with EBRT or enucleation were generally allocated to receive chemoreduction. There appeared to be some differences between the two treatment groups at baseline: patients in the group who did not receive chemoreduction were more likely to have the sporadic form of the disease and were older at diagnosis. In addition, there was a higher proportion of patients who were defined as at risk in the chemoreduction group compared with the comparison group. Patients were not matched for relevant prognostic variables. Results were stratified for whether patients had bilateral and/or familial disease or unilateral sporadic disease. Other potential confounding variables were not considered.

Results

In the prospective study all patients (14/14) survived in the chemotherapy group and 36 of the 37 patients survived in the comparison group.[132]

One case of trilateral retinoblastoma was observed in the retrospective study.[131] There was a statistically significant difference between the observed and expected number of cases of trilateral retinoblastoma for at-risk patients in the chemoreduction group, with fewer observed cases of retinoblastoma than would be expected, whereas in the non-chemoreduction group there was no difference: in the 99 at-risk patients administered chemoreduction, the expected number of cases of trilateral retinoblastoma was five to 15, whereas there were no events observed ($p < 0.01$); in the 18 at-risk patients not receiving chemoreduction, the expected number of events was one to three, and one event was observed.

Conclusions

It is not appropriate to compare the findings of these two studies comparing chemotherapy to no chemotherapy owing to differences in patients, treatment and outcomes assessed. It is difficult to draw meaningful conclusions from the prospective study given the small number of patients in the chemotherapy group, the lack of information about the treatment received by the comparison group and the lack of consideration of potential confounding factors.[132] In addition to the quality issues already discussed in relation to the retrospective study, longer follow-up of these patients is required. In addition, the study would have benefited from a larger sample size, as there was a small number of expected events of trilateral retinoblastoma.

Chemotherapy following enucleation compared with enucleation alone

One prospective study[107] and one retrospective study[38] compared patients who had received adjuvant chemotherapy following enucleation with patients who had received enucleation only.

TABLE 9 *Summary of studies comparing chemotherapy following enucleation with enucleation alone*

Study details	Intervention	Patients	Outcomes
Wolff *et al.*, 1981;[107] USA **Treatment period** 1977–1980	**Treatment 1** Enucleation plus adjuvant chemotherapy with cyclophosphamide and vincristine **Treatment 2** Enucleation	**Treatment 1** 43 participants (43 eyes) RE group V *n* = 43 **Treatment 2** 45 participants (45 eyes) RE group V *n* = 45 All unilateral retinoblastoma	• survival • relapse • adverse effects **Length of follow-up** *Treatment 1* At one treatment centre mean = 23 months; at the second centre mean = 22 months *Treatment 2* At one treatment centre mean = 20 months; at the second treatment centre mean = 13 months
Honavar *et al.*, 2002;[38] USA **Treatment period** 1974–1999	**Treatment 1** Enucleation plus adjuvant chemotherapy Before 1994: vincristine sulphate + doxorubicin hydrochloride + cyclophosphamide After 1994: vincristine + etoposide + carboplatin **Treatment 2** Enucleation 1 day to 2 weeks following diagnosis	**Treatment** 1 46 participants (46 eyes) RE group IVb *n* = 1; group V *n* = 45 **Treatment 2** 34 participants (34 eyes) RE group V *n* = 34 All unilateral sporadic retinoblastoma	• Presence of metastasis • Adverse effects **Length of follow-up** Median 59 months (range 12–287 months) for both groups combined

Study characteristics

Intervention

The main characteristics of both studies are detailed in *Table 9*. The two studies used different chemotherapy regimens. Information on drug dosage is contained in Appendix 6. In the retrospective study patients in the chemotherapy group received a different regimen of chemotherapy agents depending on whether they were treated before or after 1994. Twelve patients in this group also received 6–12 mg intrathecal methotrexate and 14 received EBRT. The mean length of treatment was 6.9 months (SD 1.4, range 6–12 months). In the prospective study, there was a 57-week treatment period.

Patients

Based on the RE classification, participants in the two studies had similar disease severity. In the retrospective study, information was provided on a range of other baseline tumour characteristics, indicating high risk for metastases for the two groups (see Appendix 6 for further details). A single histopathological risk factor was present in 62.5% (n = 50) of patients and 37.5% (n = 30) had more than one risk factor for metastases. Patients had no evidence of metastases at diagnosis. The median age of the group receiving chemotherapy was 34 months and the comparison group 30 months.

Outcome

Two-year survival and number of relapsed patients were the outcomes of interest in the prospective study, and the presence of metastases was the main outcome in the retrospective study.

Quality

In the prospective study 54 patients were randomly allocated to treatment, with the remaining patients not randomly allocated. The paper did not report details of how these patients were allocated. Although data for one of the outcomes of interest were reported separately for randomised and non-randomised patients, this study has been classified as a non-randomised controlled trial. No information is provided on why some of the patients were randomly allocated and others were not, leading to a high risk of selection bias. Possible confounding variables were

not considered. Nine patients were lost to follow-up in the enucleation-only group compared with three lost to follow-up and four withdrawn in the group receiving adjuvant chemotherapy. In the retrospective study, treatment allocation was based on hospital treatment protocol at the time or parental choice. Several relevant prognostic variables were identified at baseline and there were some differences between the two groups, although these appear minor. A stratified analysis was carried out based on whether patients had single or multiple baseline risk factors for metastases.

Results

In the prospective study there was no statistically significant difference in survival at 2 years between those who received adjuvant chemotherapy (87.6%) and those who did not (96%). Four patients relapsed in the chemotherapy group compared with three in the enucleation-only group. Two patients withdrew owing to generalised non-fatal reactions to cyclophosphamide. In the retrospective study, ten patients developed metastases at a median of 9 months (range 6–57 months). Significantly fewer patients in the group who received chemotherapy following enucleation developed metastases compared with the enucleation-only group (4.4%; $n = 2$, versus 23.5%, $n = 8$, respectively, $p = 0.02$). Kaplan–Meier estimates showed that 96% of patients who received adjuvant therapy would remain free of metastasis at 10 years following enucleation compared with 76% of those who did not receive adjuvant therapy (Cox proportional hazards $p = 0.03$; hazard ratio 0.175, 95% CI 0.037 to 0.824).

For patients with single risk factors no patients in the chemotherapy group and four patients in the enucleation group developed metastases. In patients with multiple risk factors, four patients in the chemotherapy group and two patients in the enucleation-only group developed metastases. The authors state that none of the patients in this series suffered irreversible systemic toxic effects with either of the drug regimens.

Conclusions

These two studies were not directly comparable owing to differences in study design, treatment regimen and outcomes assessed. One study found no improvement in survival with chemotherapy following enucleation. However, this was from a poor quality controlled trial. Chemotherapy following enucleation was more effective than enucleation alone in the prevention of metastases in the second study, which was retrospective. In addition to the limitations of the treatment allocation, it is likely that the use of two different chemotherapy treatment regimens, received by patients depending on the date of treatment, as well as the adjuvant treatments received by the chemotherapy group, may have had a confounding effect in this study. The small group sizes did not permit investigation of these factors.

Chemotherapy and radiotherapy compared with 'no treatment'

One retrospective study compared patients who had received radiotherapy and/or chemotherapy with those who had received local therapy, following enucleation of the other eye.[116]

Study characteristics

Intervention

Table 10 summarises the main study characteristics. The group who had only local therapy following enucleation, or who had orbital implant exposure before receiving chemotherapy or radiotherapy, were classified as having untreated sockets. Patients who received radiotherapy and/or chemotherapy, before or at the time of exposure, were classified as having treated sockets. EBRT was in the form of a whole-eye or lens-sparing technique. Chemotherapy was received as first line (6–8-week courses at 3-week intervals) or second line treatment (4 courses).

Patients

The study included 107 patients with unilateral and bilateral retinoblastoma in the analysis. Only patients with a minimum follow-up of 3 months were included. Median age at diagnosis was 19 months (range 0–136 months) and median age at enucleation was 24 months (range 1–54 months).

Outcome

The rate of exposure of orbital implants inserted following enucleation was assessed.

Quality

The method of treatment allocation was only partly described, but appeared to be on the basis of clinical indication. Clinical indications were reported for chemotherapy only. The only relevant prognostic variable identified was form of retinoblastoma. Patients were not matched for relevant prognostic/confounding variables and it was unclear whether the intervention groups were comparable at baseline.

TABLE 10 *Summary of study comparing different treatments following enucleation*

Study details	Intervention	Patients	Outcomes
Lee *et al.*, 2000;[116] UK **Treatment period** 1993–1997	**Treatment 1** 'Untreated' Cryotherapy, thermotherapy or brachytherapy **Treatment 2** Treated Chemotherapy and/or radiotherapy EBRT 40–50 Gy Vincristine, etoposide and carboplatin	**Treatment 1** 57 participants (57 sockets) **Treatment 2** 50 participants (50 sockets) Unilateral sporadic $n = 70$; unilateral familial $n = 2$; bilateral sporadic $n = 33$; bilateral familial $n = 3$	• Rate of exposure of orbital implants **Length of follow-up** Median 21.6 months (range 3–55 months for both treatment groups combined)

Results

The rate of exposure of the orbital implant in the untreated group was 20% ($n = 12$) and in the treated group was 35% ($n = 18$). No statistical analyses were carried out in relation to this set of data. Further data are reported in the paper examining the effects on rate of orbital implant exposure of radiotherapy and chemotherapy, implant type and covering, age at enucleation, gender, diagnosis, surgeon and implant size. Radiotherapy and chemotherapy did not appear to have an effect on rate of exposure.

Conclusions

It is not possible to draw any strong conclusions from the findings of this study. Owing to the way in which patients were allocated to treatment group, it is unclear whether differences between the two treatment groups may have influenced the rate of exposure of the orbital implant in this study.

Comparison of different chemotherapy regimens

Two prospective studies compared two different chemotherapy regimens in patients with intraocular retinoblastoma[132,134] and one retrospective study compared two different chemotherapy regimens for the treatment of extraocular retinoblastoma.[130]

Study characteristics

Intervention

The main study characteristics of the prospective studies are detailed in *Table 11*. Both prospective studies compared six-cycle chemoreduction with a shorter cycle of chemoreduction, specified as fewer than six cycles in one study, although the precise number of cycles administered is not specified,[133] and two cycles in the other study.[134] In the latter study both groups received adjunctive treatments. In the former study six-cycle and fewer than six-cycle chemoreduction were compared with and without adjunctive treatment. Patients from both studies were treated at the same centre, during the same period, and the same chemoreduction treatment protocols were used. Vincristine sulphate, etoposide and carboplatin were used (details of doses are given in Appendix 6). Focal treatment following chemoreduction included laser photocoagulation, transpupillary thermotherapy, cryotherapy and plaque radiotherapy. Shields and colleagues also reported the use of EBRT or enucleation for diffuse vitreous or subretinal seeds.[133]

Table 12 summarises the two chemotherapy regimens used in the retrospective study,[130] with further details on dose and number of treatments available in the data extraction tables (Appendix 6). For patients receiving treatment from 1987 to 1991, patients with class I tumours (based on the CCG Classification for Extraocular Retinoblastoma) were given cyclophosphamide and vincristine; patients with class II–V tumours were given induction therapy with cisplatin and teniposide. For patients without disease progression or recurrence after three cycles, this was followed by a regimen of cisplatin and teniposide alternating with doxorubicin, cyclophosphamide and vincristine. For patients treated from 1992 to 2000, induction therapy for all patients was ifosfamide and etoposide. For patients without disease progression or recurrence after three cycles this was followed by ifosfamide and etoposide alternating with cisplatin and tenoposide. Intrathecal therapy, for both groups, consisted of methotrexate and cytarabine and

TABLE 11 *Summary of prospective studies comparing chemotherapy regimens*

Study details	Intervention	Patients	Outcomes
Shields *et al.*, 1997;[133] USA **Treatment period** 1994–1996	**Treatment 1** Chemoreduction of fewer than six cycles without adjuvant therapy **Treatment 2** Chemoreduction of fewer than six cycles with adjuvant therapy **Treatment 3** Six cycles of chemoreduction without adjuvant therapy **Treatment 4** Six cycles of chemoreduction with adjuvant therapy	**Treatments 1 and 2** 18 participants (25 eyes) *Vitreous seeding* Treatment 1 $n = 0$; treatment 2 $n = 13$ *Subretinal seeding* Treatment 1 $n = 6$; treatment 2 $n = 8$ **Treatments 3 and 4** 14 participants (27 eyes) *Vitreous seeding* Treatment 3 $n = 4$; treatment 4 $n = 7$ *Subretinal seeding* Treatment 3 $n = 6$; treatment 4 $n = 8$ RE group Ia $n = 1$; group II $n = 5$; group III $n = 9$; group IV $= 1$; group V $n = 36$ Bilateral $n = 19$; unilateral $n = 13$	• Retinal tumour size • Retinal tumour recurrence • Vitreous seed recurrence • Subretinal seed recurrence • Final ocular management **Length of follow-up** *Treatments 1 and 2* Mean 19 months *Treatments 3 and 4* Mean 16 months
Guenduez *et al.*, 1998;[134] USA **Treatment period** 1994–1996	**Treatment 1** Two-cycle chemoreduction with adjunctive therapy **Treatment 2** Six-cycle chemoreduction with adjunctive therapy	**Treatment 1** 13 participants (16 eyes) RE group Va $n = 11$; group Vb $n = 5$ **Treatment 2** 9 participants (11 eyes) RE group Va $n = 8$; group Vb $n = 3$	• Number of patients requiring EBRT • Eye salvage rate **Length of follow-up** Mean 24 months (median 25 months; range 20–32 months)

dexamethasone. The external beam radiation dose was given concomitantly to the chemotherapy schedule, in both treatment groups, using 40–50 Gy in 23 fractions of 2 Gy each (median total dose 46 Gy in 23 fractions of 2 Gy) in patients with class II–V eyes. None of the patients with class I tumours received orbital EBRT. Patients with class I and II tumours were given enucleation at the time of diagnosis followed by the respective chemotherapy schedules. Patients with class III–V received enucleation after three cycles of the induction chemotherapy regimen.

Patients

The prospective studies included 32[133] and 22[134] patients. Shields and colleagues[133] included newly diagnosed patients with RE Group I–V eyes, with the majority of eyes classified as group V. Guenduez and colleagues[134] included only patients with RE group V eyes; it is not specified whether these were newly diagnosed patients. In the latter study the mean age of patients at diagnosis was 16 months (median 11 months, range 2–46 months) in the two-cycle chemoreduction group and 18 months (median 12 months, range 3–42 months) in the six-cycle chemoreduction group.[134] The other study reported a mean age at presentation of 13 months (median 12 months; range 1–46 months) for both treatment groups combined.[133] Patients from both studies were treated in the same centre. Given the overlap in treatment period it is possible that some patients may be reported on in both studies. The authors do not state whether this is the case.

All participants in the retrospective study had newly diagnosed extraocular retinoblastoma.[130] The majority of patients in both treatment groups

TABLE 12 *Summary of retrospective study comparing chemotherapy regimens*

Study details	Intervention	Patients	Outcomes
Antoneli, 2003;[130] Brazil **Treatment period** *Treatment 1* 1987–1991 *Treatment 2* 1992–2000	**Treatment 1** Cisplatin, teniposide, vincristine, doxorubicin and cyclophosphamide **Treatment 2** Cisplatin and teniposide with alternating courses of ifosfamide and etoposide EBRT was received concomitantly in both groups	**Treatment 1** 43 participants (54 eyes) CCG classification Class I–III $n = 36$; class IV–V $n = 7$ 11 bilateral; 32 unilateral **Treatment 2** 40 participants (49 eyes) CCG classification Class I–III $n = 33$; class IV–V $n = 7$ 9 bilateral; 31 unilateral	• Survival • Disease-free survival **Length of follow-up** Not specified. 3- and 5-year survival curves were calculated

had unilateral retinoblastoma. Mean age at diagnosis was 29.7 months for the earlier treatment group and 30.8 for the most recent treatment group. The age range for both groups combined was 2–145 months. Patients were treated at a single centre.

Outcomes

The outcomes in one prospective study were concerned primarily with tumour and seed recurrence,[133] whereas in the other study the main outcomes were requirement for EBRT and eventual enucleation.[134]

Five-year overall survival and 3- and 5-year disease-free survival were reported in the retrospective study.[130] Five-year overall survival was also reported for unilateral patients only.

Quality

In both prospective studies, treatment allocation was according to hospital protocol: the treatment protocol was initially for two cycles of chemotherapy and this was later changed to a six-cycle protocol to achieve better long-term control. Choice of focal treatment was on an individual tumour basis. Relevant prognostic variables were identified in both studies. In one of the studies there were no statistically significant differences between the two treatment groups with respect to the baseline characteristics assessed.[134] It was unclear in the other study whether the treatment groups were similar at baseline, although patients who received chemoreduction of fewer than six cycles with no adjuvant therapy had no vitreous seeding and, in this respect, differed from all the other patient groups.[133] However, this study did carry out a stratified analysis depending on pretreatment status for seeding.

In the retrospective study, chemotherapy regimen received by patients was determined by the year in which they received treatment, as the therapy used changed over time.[130] This study is susceptible to factors such as changes in other aspects of care and diagnosis having a confounding effect with treatment. Relevant prognostic variables were identified and the two groups were similar at baseline for age, tumour classification and laterality. The length of follow-up for the individual treatment groups was unclear. Different lengths of patient follow-up were adjusted for using Kaplan–Meier survival curves. Only very limited analyses were carried out taking into consideration potential confounding variables; overall survival was reported by baseline tumour classification.

Results

Guenduez and colleagues[134] found no significant difference between the two treatment groups in the number of patients requiring EBRT (75%, $n = 12$, of the two-cycle chemoreduction eyes required EBRT versus 36%, $n = 4$, of six-cycle eyes, $p = 0.28$). The global salvage rate was significantly lower in the two-cycle chemoreduction group for the group that did not receive EBRT (0% global salvage compared with those who did (75% global salvage, $n = 9$, $p = 0.03$). In the six-cycle chemoreduction group the rate of global salvage was similar in the EBRT (75%, $n = 3$) and no EBRT (71%, $n = 5$) groups.

Shields and colleagues[133] found no statistically significant differences between treatment groups in retinal, vitreous or subretinal seed recurrence when patients were included in the analysis, regardless of pretreatment status for seeding (see Appendix 6 for rate of recurrence in each

treatment group). There were significant differences between treatments for vitreous seed and subretinal seed recurrence for patients who had this form of seeding before treatment ($p = 0.04$ when the treatments were compared for the 24 eyes with vitreous seeding at baseline; $p = 0.003$ when the treatments were compared for the 28 eyes with subretinal seeding at baseline). For both outcomes the recurrence was higher in both chemotherapy groups among those patients who had not received adjunctive therapy; however, this analysis was based on very small group sizes.

Conclusions

Although the data were gathered prospectively in these studies, both studies have limitations in common with other studies in this review, which prevent firm conclusions being drawn from the findings. The key issue is in relation to treatment allocation: first, period of treatment determined the number of cycles of chemoreduction received, effectively historical controls were used; and second, whether or not patients received adjunctive therapy following chemoreduction was dependent on tumour status at that time and tumour status is related to future outcome. In addition, the analyses were based on a small number of events.

In the retrospective study of patients with extraocular retinoblastoma, there were no statistically significant differences between the two treatment groups in 5-year overall survival (55.1% versus 59.4% for the older and new treatment, respectively) or disease-free survival (59.6% versus 69.5% for the older and new treatment, respectively).[130] Within each of the treatment groups, overall survival was significantly poorer in patients with class IV–V compared with class I–III tumours, although these analyses included a relatively small number of class IV–V patients (see Appendix 6).

Enucleation compared with radiotherapy

Four retrospective studies compared enucleation and radiotherapy.[114,118,120,125]

Study characteristics

Intervention

The main study characteristics are detailed in *Table 13*. One study compared three different types of radiotherapy with enucleation,[125] one compared enucleation with EBRT (teletherapy) and both treatments combined,[118] one compared enucleation with radiotherapy (type of radiotherapy not specified), both treatments combined and local therapy,[120] and one compared enucleation with enucleation combined with EBRT and EBRT only.[114] No adjunctive therapy was reported for the treatment groups in three studies.[114,118,120] In the remaining study some patients in the three radiotherapy treatment groups also received chemotherapy and orbital radiation, and some patients who underwent unilateral enucleation also received photocoagulation, with or without cryotherapy of the contralateral eye.

Patients

The number of study participants ranged from 54 to 99. Two studies included patients with bilateral retinoblastoma only,[120,125] and two included bilateral and unilateral patients.[114,118] In one study, the majority of participants had extraocular extension or metastasis.[118] Only one study provided information on age at diagnosis: the median age at diagnosis was 13 months (range 1 day to 6.9 years) for the whole group, although age was not reported by treatment group.[114] Patients had been treated in a single clinic in three studies[114,118,120] and in the final study it was unclear.[125]

Outcome

The four studies reported diverse outcomes. One study reported survival at less than 1 year, 1–3 years, 3–5 years and more than 5 years.[118] The remaining studies were concerned with the side-effects of treatment.[114,120,125] One assessed bony orbital growth using CT,[114] one assessed midface growth inhibition based on the evaluation of six midfacial regions using a rating scale from 0 (no inhibition) to 5 (extreme inhibition),[120] and one reported height of participants normalised by expressing SDS according to the mean for age and gender of participants reported as mean height score and standard deviation.[125]

Quality

Only one of the studies explicitly reported how patients were allocated to treatment groups.[118] Patients were allocated to treatment group according to stage of disease based on Miller classification: surgery alone was undertaken only for stages I and II disease (quiescent and glaucomatous stages), stage III patients (extraocular extension) were treated with surgery followed by brachytherapy and stage IV patients (metastasis), where the tumour was inoperable, were treated by brachytherapy alone. This study was also the only study to report any information on prognostic variables, although only disease

TABLE 13 *Summary of studies comparing enucleation and radiotherapy*

Study details	Intervention	Patients	Outcomes
Srivastava *et al.*, 1984;[118] India **Treatment period** 1970–1979	**Treatment 1** Radiotherapy alone using ^{60}Co teletherapy 35–40 Gy **Treatment 2** Enucleation **Treatment 3** Enucleation and ^{60}Co teletherapy 35–40 Gy	**Treatment 1** Number allocated not stated Data reported on 18 patients Miller classification All stage IV **Treatment 2** Number allocated not stated Data reported on 3 patients Miller classification All stage II **Treatment 3** Number allocated not stated Data reported on 14 patients Miller classification All stage III Bilateral $n = 59$; unilateral $n = 5$[a]	• Survival **Length of follow-up** *Treatment 1* Range <1 year to >5 years *Treatment 2* Range 3 to 5 years *Treatment 3* Range <1 year to >5 years
Mohr *et al.*, 1990;[120] Germany **Treatment period** 1965–1983	**Treatment 1** Local therapy (cryotherapy or laser techniques) **Treatment 2** Enucleation **Treatment 3** Radiotherapy **Treatment 4** Enucleation and radiotherapy	**Treatment 1** 15 facial halves **Treatment 2** 67 facial halves **Treatment 3** 68 facial halves **Treatment 4** 19 facial halves All bilateral retinoblastoma	• Midface growth inhibition **Length of follow-up** 15.5 years
Hauffa *et al.*, 1995;[125] Germany **Treatment period** Not stated	**Treatment 1** Radiotherapy using X-ray Median dose: 44 Gy (range 36–84 Gy) **Treatment 2** Radiotherapy using ^{60}Co or ^{137}Cs isotopes Median dose: 59 Gy (range 40–127 Gy) **Treatment 3** Radiotherapy 5.7 MeV linear lateral accelerator or two opposing lateral temporal fields Median dose: 42 Gy (range 40–48Gy) **Treatment 4** Enucleation	**Treatment 1** 37 participants **Treatment 2** 12 participants **Treatment 3** 31 participants **Treatment 4** 12 participants All bilateral retinoblastoma	• Height **Length of follow-up** 14.8 years (range 5.3–24.2 years)

continued

TABLE 13 *Summary of studies comparing enucleation and radiotherapy (cont'd)*

Study details	Intervention	Patients	Outcomes
Kaste *et al.*, 1997;[114] USA **Treatment period** 30-year treatment period; dates not stated	**Unilateral disease** *Treatment 1* Enucleation *Treatment 2* Enucleation and EBRT **Bilateral disease** *Treatment 1* Unilateral enucleation and contralateral EBRT *Treatment 2* Bilateral EBRT *Treatment 3* Bilateral enucleation and bilateral EBRT *Treatment 4* Unilateral enucleation and bilateral EBRT EBRT was given in doses of 22.5–44 Gy across all treatment groups	**Unilateral disease** *Treatment 1* 24 participants *Treatment 2* 2 participants **Bilateral disease** *Treatment 1* 18 participants *Treatment 2* 3 participants *Treatment 3* 2 participants *Treatment 4* 4 participants	• Orbital volume **Length of follow-up** Median 7.5 years (range 4.9–25.8 years)

[a] This information refers to the total 64 patients included in the study, although outcome data were reported on 35 patients only; 54/64 patients were followed up, of whom 19 had incomplete treatment or refused treatment.

stage was reported.[118] None of the studies was matched for relevant prognostic/confounding variables or carried out any statistical analysis to investigate the effect of potential confounding variables on treatment outcomes. It was unreported or unclear whether the treatment groups were comparable at baseline.[114,118,120,125]

Results

In the study reporting survival, the outcome reporting was somewhat unclear. It appears that none of the patients who received enucleation only survived, none of the four patients receiving brachytherapy who were followed for more than 5 years survived, and three of the six patients receiving both treatments combined who were followed for more than 5 years survived. Outcomes for patients followed for shorter periods are detailed in the data extraction table (Appendix 6).[118] Given that patients receiving radiotherapy only had metastasis, whereas the combined treatment group was assessed as having less severe disease, there was a strong possibility of confounding between baseline disease severity, treatment received and outcome.

Enucleation combined with radiotherapy appeared to cause the most severe growth inhibition, although a statistical analysis is not reported for total midface growth inhibition.[120] This information is reported for six subscales (data have not been extracted).

The majority of patients had normal height (84 of 92 patients).[125] The authors state that median height did not differ significantly between patients treated with radiotherapy and enucleation (see data extraction table in Appendix 6 for further details). Apart from the problems with the study design, this study may have been underpowered to detect differences between groups.

Forty-eight of 54 patients had orbital volume asymmetry.[114] It is not possible to make meaningful comparisons for the two treatment groups with unilateral disease, as there were only two patients in one of the treatment groups. Similarly, with bilateral disease, apart from one treatment group of 18 patients the treatment groups were extremely small.

Conclusions

This group of studies comparing radiotherapy with enucleation is diverse in relation to the outcomes measured. All of the studies have significant problems with validity, as outlined above. Given the diversity of outcomes and lack of information on the patient population by which to assess their similarity, their findings are best considered individually.

Chapter 5

Discussion and conclusions

Clinical effectiveness

Treatment outcomes in children with retinoblastoma were investigated to provide the evidence base on clinical effectiveness. The main conclusion of this systematic review is that the evidence base for effectiveness of treatments for childhood retinoblastoma is extremely limited. Although many of the studies reported high levels of treatment success, the relative effectiveness and adverse effects of treatment were unclear.

One poor-quality non-randomised controlled trial was found. The remaining comparative studies were observation design. Almost all of these were retrospective. The studies had significant problems with internal validity. Owing to the considerable limitations of the evidence available, it is not possible to draw meaningful conclusions about the relative effectiveness of different treatment approaches for childhood retinoblastoma.

The highest number of studies found was in relation to radiotherapy, which is to be expected, as this was one of the earliest treatments for childhood retinoblastoma. Radiotherapy or chemotherapy was the comparator in the majority of studies. However, only a small number of studies comparing different radiotherapy techniques and different chemotherapy regimens was available. There were very few studies available on focal treatments, with only plaque radiotherapy or brachytherapy and photocoagulation being assessed as individual treatments. There were no comparative studies assessing the effectiveness of cryotherapy, thermotherapy or chemothermotherapy. In all the studies of local treatments, the comparator was radiotherapy, with no studies comparing different local treatments with each other.

Outcomes

Although tumour control and survival are the key aims of treatment for childhood retinoblastoma, other outcomes such as useful vision, cosmetic implications and side-effects, as well as long-term complications, are clinically regarded as important factors in the decision about treatment options.

However, apart from the data on risk of SPTs following radiotherapy, few data on adverse effects of treatment interventions for childhood retinoblastoma were available from the included studies. Only a small number of studies reported data on adverse effects and it was not always clear how systematically these data had been gathered. Data on cosmetic complications and visual acuity were poorly reported. In addition, none of the studies considered the impact of treatment on children's general development; specifically, the emotional and psychological consequences of the various treatments.

Limitations of the evidence

None of the studies had the benefits of randomised allocation with allocation concealment and blinding of clinicians, participants and outcome assessors, and they were therefore susceptible to selection bias and measurement bias. There was a high risk of selection bias in both the prospective and retrospective studies. This is introduced when patients allocated to a treatment group have systematic differences to the comparison treatment group in terms of prognostic variables such as disease severity. All of the studies were susceptible to detection bias, introduced when there is no blinding of outcome assessors to protect against systematic differences between treatment groups in how outcomes are assessed. The difficulties of blinding outcome assessment in this field are acknowledged; nevertheless, lack of blinding does introduce the possibility of detection bias. The studies were also susceptible to performance bias. This is introduced when there are systematic differences in the care provided (apart from the intervention of interest) owing to factors such as lack of blinding and standardisation of the care protocol. The retrospective studies were particularly susceptible to performance and measurement bias as they were less likely to have a study protocol specifying the intervention and outcome assessments than were prospective studies.

The main distinction between randomised and non-randomised studies is the way in which participants are allocated to a treatment group

and therefore the risk of selection bias. The circumstances in which, and the extent to which, observational studies are susceptible to bias are not fully understood.[40] However, the extent to which prognosis influences selection for a particular treatment as well as eventual outcome may be an important determinant of the extent of bias present.[40] Based on this, the studies included in the review are highly susceptible to this form of bias. Over half of the included studies did not describe how patients were allocated to a treatment intervention, although by implication it is likely that treatment received depended on the particular treatment protocol in use at the clinic at the time of the study. Therefore, a range of factors may have had an influence on treatment allocation, including disease severity, age of patient, previous treatment, clinician preference and parental preference. This may have resulted in systematic differences between treatment groups. In other studies treatment allocation was explicitly on the basis of disease severity. Again, the additional influence of factors such as the physician's perception of the patient's prognosis influencing allocation cannot be discounted.[139] Other studies used historical controls. This method is also associated with bias in the assessment of treatment effects, often, but not always, in favour of the new treatment.[40,140] When studies using historical and randomised controls were compared for the same therapy, differences between the results of the two study designs were mainly due to historical controls having poorer outcome than randomised controls, leading to the conclusion that, owing to biases in patient selection, outcome was weighted in favour of the new treatment.[140] This was partly supported by a more recent investigation, although there was evidence that, when the case-mix of patients being considered for treatment changes over time, there can also be an underestimation of the effectiveness of the new therapy.[40]

The comparability of treatment groups at baseline was established in only a small number of studies. Attempts to take into account the possible confounding effect of factors such as disease severity were mainly limited to reporting results by RE classification, with no statistical comparisons between groups. There is evidence that commonly used methods to deal with potential confounding due to variations in case-mix in cohort studies are not always successful. This applies even to more sophisticated approaches than stratified analysis.[40]

The level of analysis varied between studies, with some reporting results by eye and others reporting results by child. There were studies including more than one eye per patient in the analysis that appeared to carry out the analysis as though the two eyes from the one individual were independent data. By not taking into account the potential correlation between eyes in individuals, falsely precise estimates of a treatment effect may be generated.[141,142]

Other sources of bias in individual studies were different lengths of follow-up for the treatment groups of interest and individual treatment groups not receiving a standard treatment. A small number of studies had very different lengths of follow-up for the two treatment groups. Consequently, there was a greater likelihood of events, such as relapse, being observed in the group with longer follow-up. Many of the remaining studies did not report length of follow-up separately for the different treatment groups. Therefore, it was not possible to assess whether there were similar lengths of follow-up in the treatment groups being compared. In relation to standard treatment, in some studies radiotherapy and chemotherapy treatment was administered using different techniques or regimens in an individual treatment group,[38,76,112] while in other studies patients in an individual treatment group received either EBRT or brachytherapy.[126,127] Some bias in treatment allocation may have occurred in these groups. In addition, many of the studies were carried out over considerable periods. The length of follow-up in studies investigating incidence of SPTs ranged from 27 to 52 years. While the long-term follow-up in such studies is valuable, the actual treatment administered and important prognostic variables related to care may change over time. Apart from a few studies where the treatment period was 1 and 2 years long, the length of time in which patients were eligible for enrolment in the studies ranged from 4 to 30 years. A number of changes may take place in studies enrolling patients over such a long duration, leading to systematic and non-systematic bias: how the intervention is administered over time, other aspects of care, the quality of documentation of outcome and adverse effects, the personnel assessing outcome, the types of patients receiving treatment at the centre, and the physicians' views and preferences about treatments and associated indications for treatment.

An additional potential limitation of the evidence presented relates to its external validity; that is, how representative patients in the included studies were of all retinoblastoma patients. Specialist centres in different parts of the world may have

different treatment protocols, and are perhaps more likely to treat more severe and complex cases of retinoblastoma, than other hospitals. It has been proposed that those patients with bilateral hereditary retinoblastoma may have a greater risk of treatment-related side-effects, and may therefore be overrepresented at specialist centres.[6] In addition, treatment outcomes may be more favourable in specialist centres. It was not possible to determine how many of the included studies were of patients attending a specialist centre.

Many studies were also poorly reported. Aspects that were poorly reported included the treatment regimens used, previous treatments received by patients for their retinoblastoma, the clinical condition of patients, length of follow-up of individual treatment groups and precise details of how outcome was defined and/or measured. Dropouts were poorly reported, as was the number of exclusions in studies that only included patients for whom full sets of data were available. Study design was also poorly reported.

Limitations of the review

When it became apparent from the searches that no controlled trials were available for inclusion in this systematic review, there was much discussion among the team about the appropriateness of including observational studies. It could be argued that it is inappropriate to include observational studies of treatment interventions in a systematic review because of the potential for bias. If such an approach had been taken, the review would have included no studies. It was felt that this would not be a helpful approach for clinicians. The view was taken that in the absence of more robust study designs the most useful approach was to include and appraise the best available evidence.

Definitions of cohort studies vary.[143–145] The decision was made to include only studies with clear comparison groups as, effectively, some of the studies that appeared to be a comparative cohort design were arguably case series with subgroup analysis of different treatment interventions. A definition of what was meant by 'clear comparison group' was developed. Despite this, some of the studies required considerable discussion among the reviewers as to whether they should be included. Therefore, the appropriateness of some of the included studies may be open to debate in terms of whether they had a clear comparison group. However, the removal of any individual study or group of studies would not alter the overall findings and conclusions of this review.

Conclusions

Implications for practice

In the authors' opinion, the evidence base is not sufficiently robust to provide clear guidance for clinical practice.

Recommendations for future research

Ideally, good quality RCTs assessing the effectiveness of different treatment options for childhood retinoblastoma are required. Research is required on all treatments used. Given the rarity of childhood retinoblastoma, the lack of RCTs is perhaps not surprising. The one study identified that was designed as an RCT closed early owing to slower accrual than expected and not all the participants were randomly allocated to treatment.[107] Ethical issues and the feasibility of recruiting enough patients to a trial are likely to be particularly important considerations in this clinical area. However, RCTs are the most robust form of evidence for clinical effectiveness of treatment interventions, and serious consideration needs to be given to ways of achieving sufficient patient numbers for trials, for example, through national and international collaboration.

Where RCTs are not feasible, for ethical or practical reasons, or where the outcome of interest is a rare event that may only occur in the long term (such as an SPT), only non-randomised studies that are prospective should be given consideration, owing to the generally higher risk for bias in retrospective studies. Where randomisation is not feasible, all the methodological characteristics of a well-designed RCT, other than the randomisation, should be present.[146] Consideration needs to be given to the most appropriate ways of keeping bias to a minimum. In particular, to reduce the risk of confounding due to allocation by clinical indication, studies should compare treatment effectiveness in patients with similar disease severity rather than compare patients of mixed disease severities. This could be achieved by including only patients with similar disease severity or by a priori stratification of patients with mixed disease severities.

To improve comparability between studies, it would also be helpful if standardised treatment protocols and outcomes could be agreed within the clinical field. In addition to tumour control

and survival, other clinically important outcomes should be considered, including useful vision, cosmesis and quality of life. These outcomes should also include relevant adverse events or side-effects of treatment with formalised and standardised forms of measurement.

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Contribution of authors

Catriona McDaid (Research Fellow) was the lead reviewer. She was involved in the protocol production, selection of trials, and data extraction and synthesis, and was responsible for writing the report. Suzanne Hartley (Research Fellow) was involved in protocol production, selection of trials, data extraction and synthesis, and writing sections of the report. She read and commented on various drafts. Anne-Marie Bagnall (Research Fellow) was involved in protocol production, selection of trials, data extraction and synthesis. She read and commented on various drafts. Gill Ritchie (Information Officer) devised the search strategy and carried out the literature searches, and wrote the search methodology sections of the report. Kate Light (Information Officer) maintained the database and carried out additional searching. Rob Riemsma (Reviews Manager) was involved in protocol production, gave input at various stages, and read and commented on various drafts.

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Appendix 1

Classification systems used for retinoblastoma

TABLE 14 *Reese–Ellsworth classification for intraocular retinoblastoma*[11]

Stage of disease	Tumour characteristics
Group I: very favourable prognosis	a: Solitary tumour, smaller than 4 disc diameters in size, at or behind the equator b: Multiple tumours, none greater than 4 disc diameters in size, all at or behind the equator
Group II: favourable prognosis	a: Solitary tumour, 4–10 disc diameters in size, at or behind the equator b: Multiple tumours, 4–10 disc diameters in size, all at or behind the equator
Group III: doubtful prognosis	a: Any lesion anterior to the equator b: Solitary tumour, larger than 10 disc diameter, behind the equator
Group IV: unfavourable prognosis	a: Multiple tumours, some greater than 10 disc diameters b: Any lesion extending anteriorly to the ora serrata
Group V: very unfavourable prognosis	a: Massive tumours involving more than half of the retina b: Vitreous seeding

TABLE 15 *International Classification for Intraocular Retinoblastoma*[4]

Stage of disease	Tumour characteristics
Group A: small intraretinal tumours away from fovea and disc	All tumours are 3 mm or smaller, confined to the retina, and are located further than 3 mm from the fovea and 1.5 mm from the optic disc
Group B: all remaining discrete tumours confined to the retina	All tumours confined to the retina not in group A Tumour-associated subretinal fluid less than 3 mm from the tumour with no subretinal seeding
Group C: discrete local disease with minimal subretinal or vitreous seeding	Tumour(s) are discrete Subretinal fluid, present or past, without seeding, involving up to one-quarter of the retina Local subretinal seeding, less than 3 mm (2 disc diameters) from the tumour Local fine vitreous seeding close to discrete tumour
Group D: diffuse disease with significant vitreous or subretinal seeding	Tumour(s) may be massive or diffuse Subretinal fluid, present or past, without seeding, involving up to total retinal detachment Diffuse subretinal seeding, may include subretinal plaques or tumour nodules Diffuse or massive vitreous disease, may include 'greasy' seeds or avascular tumour masses
Group E: presence of any one or more of these poor prognosis features	Tumour touching the lens, neovascular glaucoma, tumour anterior to anterior vitreous face involving ciliary body or anterior segment, diffuse infiltrating retinoblastoma, opaque media from haemorrhage, tumour necrosis with aseptic orbital cellulitis, or phthisis bulbi

TABLE 16 *Gabrowski and Abramson classification for intraocular and extraocular retinoblastoma*[17]

Stage	Tumour localisation
I	Intraocular disease
	a: retinal disease
	b: extension to the lamina cribrosa
	c: uveal extension
II	Orbital disease
	Orbital tumour
	a1: scattered episcleral cells
	a2: tumour mass
	Optic nerve
	b1: distal nerve; line of section and meninges clear
	b2: tumour at line of section or in the meninges
III	Intracranial metastasis
	a: positive bone marrow alone
	b: focal bone lesions with or without positive marrow
	c: other organ involvement

Appendix 2

Treatments used for retinoblastoma

TABLE 17

Treatment	Indication	Technique
Enucleation	Enucleation is used to treat advanced disease with a remote chance of salvaging useful vision. These include cases with massive tumours or retinal detachment and those with involvement of local extension to the optic nerve, choroid or orbit. Eyes with pars plana seeding, secondary glaucoma or involvement of the anterior or chamber may also be managed with enucleation.[35,147–149] Enucleation is also used in patients who fail to respond to other methods[4,35] In patients with bilateral retinoblastoma the eye with the most advanced disease may be enucleated and the contralateral eye treated with more conservative methods.[4,150] Bilateral enucleation is rare and is indicated when both eyes have advanced disease, where efforts to salvage eyes may place the child at increased risk of developing systemic metastasis[4,35,150] Adjuvant irradiation or chemotherapy may be required if the patient is at risk of metastatic disease[13]	The entire eye is surgically removed along with a section of the optic nerve.[2,35,151] Orbital implants are positioned at the time of surgery to improve the cosmesis and subsequent prosthetic motility Patients are examined and monitored to allow for assessment of the need for adjuvant treatment to prevent metastatic disease and to detect orbital recurrence of the tumour[13,35,151]
External beam radiotherapy	EBRT is commonly used for the treatment of tumours that are greater than 15 mm in diameter. It can be used where the tumour has extended into the orbit, or is located near the optic disc or fovea. Multiple tumours and the presence of vitreous seeding can be treated with EBRT[3,152] EBRT is commonly used for the treatment of recurrent tumours following initial treatment focal therapy or chemotherapy that cannot be controlled by focal therapy[4]	Various techniques are used to deliver EBRT, and are influenced by the stage of the tumour The use of the lens-sparing temporal portal technique reduces the occurrence of radiation-induced cataracts, but does provide irradiation to the anterior. The anterior technique is required to irradiate the ora serrata and vitreous seeding. Combinations of anterior and lateral are commonly used, with the placement of a lens block to reduce the possibility of cataract[3,4] A total dose of 35–40 Gy is commonly given in fractionated doses over a period of 4–5 weeks.[3,4] Newer modes of delivery under evaluation, including stereotactic radiotherapy and proton beam radiotherapy, are focused and aim to minimise irradiation of surrounding tissue, leading to a reduction in adverse effects[4,24]

continued

TABLE 17 *(Cont'd)*

Treatment	Indication	Technique
Brachytherapy	Brachytherapy can be used as a primary treatment for solitary unilateral or bilateral tumours less than 15 mm in diameter that are located approximately 2 mm from the optic disc or fovea, or following chemoreduction[3,147,148,151] It can be used to treat recurrent or residual tumours that are not successfully controlled by chemoreduction, photocoagulation, thermotherapy, cryotherapy or EBRT[3,4,153] It is contraindicated for tumours that have produced seeding[148,153] or in posterior tumours with involvement of the optic disc or fovea[3,4,148]	Brachytherapy involves the placement of a plaque containing radioactive isotopes (typically ^{125}I or ^{106}Ru) on the sclera at the base of the tumour until the required dose of about 35–40 Gy is delivered to the tumour apex[2–4]
Photocoagulation	Photocoagulation is indicated for tumours smaller than 4.5 mm in diameter that are confined to the retina with no evidence of seeding.[2] It can be used to treat tumours that have undergone chemoreduction, or as an additional treatment in cases initially treated with radiation or cryotherapy, or for recurrences following chemotherapy[3,4,151]	Photocoagulation involves the use of argon or diode lasers to delimit the tumour by coagulating vascular supply
Cryotherapy	Cryotherapy is indicated for the primary treatment of small tumours, typically smaller than 3.5 mm in diameter, which are located anterior to the equator near the ora serrata, or for the treatment of residual or recurrent tumours Cryotherapy is contraindicated where there is evidence of vitreous seeding	Cryotherapy involves destroying the tumour using a triple freeze–thaw technique delivered over one or two sessions
Chemotherapy	Chemotherapy can be used to reduce the size of the intraocular retinoblastoma (chemoreduction) to make it accessible to subsequent focal therapy with cryotherapy, photocoagulation or brachytherapy to ensure tumour control. Chemotherapy can also be used alone as primary treatment[4,13,35,37,106] In cases of advanced intraocular retinoblastoma chemotherapy can be combined with EBRT (chemoradiotherapy) to avoid enucleation.[37,151] Chemotherapy (with or without irradiation) is the main treatment choice for patients with extraocular or trilateral retinoblastoma[2,37]	The most commonly used chemotherapeutic drugs are vincristine, etoposide and carboplatin, with or without the addition of cyclosporine. The number of cycles varies from two to more than eight between treatment centres, although this is related to the stage of disease.[4,35] Longer courses are typically required to treat systemic retinoblastoma[2] Intracranial chemotherapy, including methotrexate, is used for the treatment of trilateral retinoblastoma and extraocular extension[37]

Appendix 3

Search strategies

The search strategy used in the scoping review was further developed to include new search terms or interventions that had been identified from the scoping exercise, and from advice received from the clinical experts consulted during the writing of the protocol. The search strategy was designed for searching the MEDLINE database (via Ovidweb) and was adapted for all other databases to account for differences in indexing terms and search syntax for each database.

All resources were searched from their inception to April 2004. There was no restriction of study by country of origin, language or publication date. Unpublished research or research published within grey literature was also sought, and Internet searches of selected websites and search engines were conducted. Attempts to identify further studies were made by contacting clinical experts and examining the bibliographies of all retrieved articles.

The following databases were searched: MEDLINE, MEDLINE In Process, EMBASE, Science Citation Index, BIOSIS, Pascal, LILACS and Cochrane Central Register of Controlled Trials (CENTRAL).

Unpublished research, ongoing trials and grey literature resources searched were: National Research Register (NRR), Current Controlled Trials, National Cancer Institute (NCI) Clinical Trials PDQ, International Cancer Research Portfolio (ICRP), System for Information on Grey Literature in Europe (SIGLE), National Technical Information Service (NTIS), Greylit Network, Dissertation Abstracts and Inside Conferences.

The following Internet resources were used: Organising Medical Networked Information (OMNI) and Google.

MEDLINE

1966 to April week 1 2004
Accessed via Ovidweb http://gateway/uk.ovid.com
Search date: 15 April 2004

1. Retinoblastoma/
2. Retinal Neoplasms/
3. retinoblastoma.ti,ab.
4. ((retina or retinal) adj2 (neoplasm$ or cancer$ or tumo?r$ or malignan$ or carcinoma$ or adenocarcinoma$ or sarcoma$)).ti,ab.
5. or/1-4
6. Eye Enucleation/
7. orbit evisceration/
8. (enucleation$ or enucleated or enucleating or exenterat$ or eviscerat$).ti,ab.
9. ((eye or eyes or eyeball$ or eye-ball$ or globe or globes or orbit or orbits) adj2 (removal or remove$ or removing or extract$)).ti,ab.
10. Brachytherapy/
11. curietherap$.ti,ab.
12. exp radiotherapy/
13. radiotherap$.ti,ab.
14. brachytherap$.ti,ab.
15. Cryotherapy/
16. cold therap$.ti,ab.
17. cryotherap$.ti,ab.
18. cryosurg$.ti,ab.
19. cryocoagulat$.ti,ab.
20. exp Light Coagulation/
21. light coagulat$.ti,ab.
22. photocoagulat$.ti,ab.
23. photoablat$.ti,ab.
24. laser coagulat$.ti,ab.
25. phototherap$.ti,ab.
26. thermocoagulat$.ti,ab.
27. radiation, Ionizing/
28. (radiation or irradiat$ or reirradiat$ or re-irradiat$ or plaque).ti,ab.
29. Hyperthermia, Induced/
30. hypertherm$.ti,ab.
31. fever therap$.ti,ab.
32. thermotherap$.ti,ab.
33. Antineoplastic Combined Chemotherapy Protocols/
34. exp Combined Modality Therapy/
35. chemotherap$.ti,ab.
36. chemothermotherap$.ti,ab.
37. thermochemotherap$.ti,ab.
38. chemoreduction.ti,ab.
39. chemoprophylaxis.ti,ab.
40. photodynamic therap$.ti,ab.
41. surgery.ti,ab.
42. Laser Surgery/

43. (laser adj2 therap$).ti,ab.
44. Carboplatin/
45. Vincristine/
46. Etoposide/
47. Cyclophosphamide/
48. cisplatin/
49. cyclosporine/
50. idarubicin/
51. doxorubicin/
52. (carboplatin or vincristine or etoposide or cyclophosphamide or cisplatin or ciclosporin$ or cyclosporin$ or idarubicin or doxorubicin or adriamycin).mp.
53. (carbosol or paraplatin or carbosin or carboplat or ribocardo or blastocarb or carbotec or displata or novoplat or nealorin or novoplatinum or ercar or paraplatin or platinwas or kemocarb).mp.
54. (oncovin or vincrin or cellcristin or farmistin or citomid or filcrin or vincasar or vintec or faulcris or pericristine or vincrisul).mp.
55. (abiposid or cehaposid or exitop or vepesid or etopophos or eposid or etopofos or celltop or eto cs or eto-gry or etomedac or riboposid or lastet or etopos or kenazol or lastet or seroposide or vp-tec or eposin or fytosid or toposar).mp.
56. (endoxin or cycloblastin or cycloblastine or enduxan or genuxal or cytoxan or procytox or caroloxan or sendoxan or cytophosphan or fosfaseron or genoxal or ledoxina or sendoxan or alkyloxan or endoxana or neosar).mp.
57. (abiplatin or platiblastin or platinol or platistine or cisplatyl or platiran or citosin or lederplatin or platinex or platosin or citoplatino or platamine or blastolem or niyaplat or plastistil or seroplatin or tecnoplatin or tisplal or platistin or faulplatin or neoplatin or placis or platistil or abiplatin or kemoplat).mp.
58. (sandimmun or neoral or neural-sandimmun or colosina or immulem or consupren or gengraf).mp.
59. (zavedos or idamycin).mp.
60. (adriamycin or myocet or adriblastin or caelyx or doxorubin or adriblastina or rubex or adriblastine or adrimedac or doxo-cell or ribodoxo or doxolem or doxotec or fauldoxo or farmiblastina or adrim or doxil or rubex).mp.
61. or/6-60
62. 5 and 61
63. animal/
64. human/
65. 63 not (63 and 64)
66. 62 not 65

MEDLINE in Process and Other Non-Indexed Citations

14 April 2004
Accessed via Ovidweb http://gateway/uk.ovid.com
Search date: 15 April 2004

1. retinoblastoma.ti,ab.
2. ((retina or retinal) adj2 (neoplasm$ or cancer$ or tumo?r$ or malignan$ or carcinoma$ or adenocarcinoma$ or sarcoma$)).ti,ab.
3. or/1-2
4. (enucleation$ or enucleated or enucleating or exenterat$ or eviscerat$).ti,ab.
5. ((eye or eyes or eyeball$ or eye-ball$ or globe or globes or orbit or orbits) adj2 (removal or remove$ or removing or extract$)).ti,ab.
6. curietherap$.ti,ab.
7. radiotherap$.ti,ab.
8. brachytherap$.ti,ab.
9. cold therap$.ti,ab.
10. cryotherap$.ti,ab.
11. cryosurg$.ti,ab.
12. cryocoagulat$.ti,ab.
13. light coagulat$.ti,ab.
14. photocoagulat$.ti,ab.
15. photoablat$.ti,ab.
16. laser coagulat$.ti,ab.
17. phototherap$.ti,ab.
18. thermocoagulat$.ti,ab.
19. (radiation or irradiat$ or reirradiat$ or re-irradiat$ or plaque).ti,ab.
20. hypertherm$.ti,ab.
21. fever therap$.ti,ab.
22. thermotherap$.ti,ab.
23. chemotherap$.ti,ab.
24. chemothermotherap$.ti,ab.
25. thermochemotherap$.ti,ab.
26. chemoreduction.ti,ab.
27. chemoprophylaxis.ti,ab.
28. photodynamic therap$.ti,ab.
29. surgery.ti,ab.
30. (laser adj2 therap$).ti,ab.
31. (carboplatin or vincristine or etoposide or cyclophosphamide or cisplatin or ciclosporin$ or cyclosporin$ or idarubicin or doxorubicin or adriamycin).mp.
32. (carbosol or paraplatin or carbosin or carboplat or ribocardo or blastocarb or carbotec or displata or novoplat or nealorin or novoplatinum or ercar or paraplatin or platinwas or kemocarb).mp.
33. (oncovin or vincrin or cellcristin or farmistin or citomid or filcrin or vincasar or vintec or faulcris or pericristine or vincrisul).mp.
34. (abiposid or cehaposid or exitop or vepesid or etopophos or eposid or etopofos or celltop or

eto cs or eto-gry or etomedac or riboposid or lastet or etopos or kenazol or lastet or seroposide or vp-tec or eposin or fytosid or toposar).mp.
35. (endoxin or cycloblastin or cycloblastine or enduxan or genuxal or cytoxan or procytox or caroloxan or sendoxan or cytophosphan or fosfaseron or genoxal or ledoxina or sendoxan or alkyloxan or endoxana or neosar).mp.
36. (abiplatin or platiblastin or platinol or platistine or cisplatyl or platiran or citosin or lederplatin or platinex or platosin or citoplatino or platamine or blastolem or niyaplat or plastistil or seroplatin or tecnoplatin or tisplal or platistin or faulplatin or neoplatin or placis or platistil or abiplatin or kemoplat).mp.
37. (sandimmun or neoral or neural-sandimmun or colosina or immulem or consupren or gengraf).mp.
38. (zavedos or idamycin).mp.
39. (adriamycin or myocet or adriblastin or caelyx or doxorubin or adriblastina or rubex or adriblastine or adrimedac or doxo-cell or ribodoxo or doxolem or doxotec or fauldoxo or farmiblastina or adrim or doxil or rubex).mp.
40. or/4-39
41. 3 and 40

EMBASE

1980 to 2004 week 15
Accessed via Ovidweb http://gateway/uk.ovid.com
Search date: 15 April 2004

1. exp Retina tumor/
2. ((retina or retinal) adj2 (neoplasm$ or cancer$ or tumo?r$ or malignan$ or carcinoma$ or adenocarcinoma$ or sarcoma$)).ti,ab.
3. retinoblastoma.ti,ab.
4. or/1-3
5. Enucleation/
6. enucleation.ti,ab.
7. evisceration/
8. (enucleation$ or enucleated or enucleating or exenterat$ or eviscerat$).ti,ab.
9. ((eye or eyes or eyeball$ or eye-ball$ or globe or globes or orbit or orbits) adj2 (removal or remove$ or removing or extract$)).ti,ab.
10. Brachytherapy/
11. exp radiotherapy/
12. curietherap$.ti,ab.
13. radiotherap$.ti,ab.
14. brachytherap$.ti,ab.
15. Cryotherapy/
16. cold treatment/
17. cold therap$.ti,ab.
18. cryotherap$.ti,ab.
19. cryosurgery/
20. cryosurg$.ti,ab.
21. cryocoagulation/
22. cryocoagulat$.ti,ab.
23. exp Laser Coagulation/
24. light coagulat$.ti,ab.
25. photocoagulat$.ti,ab.
26. photoablat$.ti,ab.
27. laser coagulat$.ti,ab.
28. exp phototherapy/
29. phototherap$.ti,ab.
30. thermocoagulation/
31. thermocoagulat$.ti,ab.
32. Ionizing radiation/
33. exp irradiation/
34. (radiation or irradiat$ or reirradiat$ or re-irradiat$ or plaque).ti,ab.
35. exp hyperthermic therapy/
36. hypertherm$.ti,ab.
37. fever therap$.ti,ab.
38. thermotherap$.ti,ab.
39. exp cancer chemotherapy/
40. Multimodality cancer Therapy/
41. chemotherap$.ti,ab.
42. chemothermotherap$.ti,ab.
43. thermochemotherap$.ti,ab.
44. chemoreduction.ti,ab.
45. Chemoprophylaxis/
46. chemoprophylaxis.ti,ab.
47. photodynamic therap$.ti,ab.
48. eye surgery/
49. Laser Surgery/
50. surgery.ti,ab.
51. (laser adj2 therap$).ti,ab.
52. Carboplatin/
53. Vincristine/
54. Etoposide/
55. Cyclophosphamide/
56. cisplatin/
57. exp cyclosporin/
58. Idarubicin/
59. Doxorubicin/
60. (carboplatin or vincristine or etoposide or cyclophosphamide or cisplatin or ciclosporin$ or cyclosprin$ or idarubicin or doxorubicin or adriamycin).mp.
61. (carbosol or paraplatin or carbosin or carboplat or ribocardo or blastocarb or carbotec or displata or novoplat or nealorin or novoplatinum or ercar or paraplatin or platinwas or kemocarb).mp.
62. (oncovin or vincrin or cellcristin or farmistin or citomid or filcrin or vincasar or vintec or faulcris or pericristine or vincrisul).mp.

63. (abiposid or cehaposid or exitop or vepesid or etopophos or eposid or etopofos or celltop or eto cs or eto-gry or etomedac or riboposid or lastet or etopos or kenazol or lastet or seroposide or vp-tec or eposin or fytosid or toposar).mp.
64. (endoxan or cycloblastin or cycloblastine or enduxan or genuxal or cytoxan or procytox or caroloxan or sendoxan or cytophosphan or fosfaseron or genoxal or ledoxina or sendoxan or alkyloxan or endoxana or neosar).mp.
65. (abiplatin or platiblastin or platinol or platistine or cisplatyl or platiran or citosin or lederplatin or platinex or platosin or citoplatino or platamine or blastolem or niyaplat or plastistil or seroplatin or tecnoplatin or tisplal or platistin or faulplatin or neoplatin or placis or platistil or abiplatin or kemoplat).mp.
66. (sandimmun or neoral or neural-sandimmun or colosina or immulem or consupren or gengraf).mp.
67. (zavedos or idamycin).mp.
68. (adriamycin or myocet or adriblastin or caelyx or doxorubin or adriblastina or rubex or adriblastine or adrimedac or doxo-cell or ribodoxo or doxolem or doxotec or fauldoxo or farmiblastina or adrim or doxil or rubex).mp.
69. or/5-68
70. 4 and 69
71. exp animal/
72. exp nonhuman/
73. 71 or 72
74. exp human/
75. 73 not (73 and 74)
76. 70 not 75

ISI Science Citation Index

1981 to April 2004
Accessed via Web of Knowledge
http://wok.mimas.ac.uk
Search date: 20 April 2004

1. TS=((retinoblastoma or retina* neoplasm* or retina* cancer* or retina* tumo?r* or retina* malignan* or retina* carcinoma* or retina* adenocarcinoma* or retina* sarcoma*) and (enucleat* or exenterat* or eviscerat* or eye* remov* or globe* remov* or orbit* remov* or eye* extract* or globe* extract* or orbit* extract* or brachytherap* or curietherap* or radiotherap* or cryotherap* or cold therap* or cryosurg* or cryocoagulat* or coagulat*))
2. TS=((retinoblastoma or retina* neoplasm* or retina* cancer* or retina* tumo?r* or retina* malignan* or retina* carcinoma* or retina* adenocarcinoma* or retina* sarcoma*) and (photocoagulat* or photoablat* or phototherap* or radiation or irradiat* or reirradiat* or plaque or thermocoagulat* or hypertherm* or fever therap* or thermotherap* or photodynamic therap* or laser therap* or surgery))
3. TS=((retinoblastoma or retina* neoplasm* or retina* cancer* or retina* tumo?r* or retina* malignan* or retina* carcinoma* or retina* adenocarcinoma* or retina* sarcoma*) and (chemotherap* or combined modality therap* or chemothermotherap* or thermochemotherap* or chemoreduction or chemoprophylaxis or carboplatin or vincristine or etoposide or cyclophosphamide or cisplatin or cyclosporin* or ciclosporin* or idarubicin or doxorubicin or adriamycin))
4. TS= ((retinoblastoma or retina* neoplasm* or retina* cancer* or retina* tumo?r* or retina* malignan* or retina* carcinoma* or retina* adenocarcinoma* or retina* sarcoma*) and (carbosol or paraplatin or carbosin or carboplat or ribocardo or blastocarb or carbotec or displata or novoplat or nealorin or novoplatinum or ercar or paraplatin or platinwas or kemocarb))
5. TS =((retinoblastoma or retina* neoplasm* or retina* cancer* or retina* tumo?r* or retina* malignan* or retina* carcinoma* or retina* adenocarcinoma* or retina* sarcoma*) and (oncovin or vincrin or cellcristin or farmistin or citomid or filcrin or vincasar or vintec or faulcris or pericristine or vincrisul))
6. TS=((retinoblastoma or retina* neoplasm* or retina* cancer* or retina* tumo?r* or retina* malignan* or retina* carcinoma* or retina* adenocarcinoma* or retina* sarcoma*) and (abiposid or cehaposid or exitop or vepesid or etopophos or eposid or etopofos or celltop or eto cs or eto-gry or etomedac or riboposid or lastet or etopos or kenazol or lastet or seroposide or vp-tec or eposin or fytosid or toposar))
7. TS=((retinoblastoma or retina* neoplasm* or retina* cancer* or retina* tumo?r* or retina* malignan* or retina* carcinoma* or retina* adenocarcinoma* or retina* sarcoma*) and (endoxan or cycloblastin or cycloblastine or enduxan or genuxal or cytoxan or procytox or caroloxan or sendoxan or cytophosphan or fosfaseron or genoxal or ledoxina or sendoxan or alkyloxan or endoxana or neosar))

8. TS =((retinoblastoma or retina* neoplasm* or retina* cancer* or retina* tumo?r* or retina* malignan* or retina* carcinoma* or retina* adenocarcinoma* or retina* sarcoma*) and (abiplatin or platiblastin or platinol or platistine or cisplatyl or platiran or citosin or lederplatin or platinex or platosin or citoplatino or platamine or blastolem or niyaplat or plastistil or seroplatin or tecnoplatin or tisplal or platistin or faulplatin or neoplatin or placis or platistil or abiplatin or kemoplat))
9. TS= ((retinoblastoma or retina* neoplasm* or retina* cancer* or retina* tumo?r* or retina* malignan* or retina* carcinoma* or retina* adenocarcinoma* or retina* sarcoma*) and (sandimmun or neoral or neural-sandimmun or colosina or immulem or consupren or gengraf or zavedos or idamycin))
10. TS=((retinoblastoma or retina* neoplasm* or retina* cancer* or retina* tumo?r* or retina* malignan* or retina* carcinoma* or retina* adenocarcinoma* or retina* sarcoma*) and (adriamycin or myocet or adriblastin or caelyx or doxorubin or adriblastina or rubex or adriblastine or adrimedac or doxo-cell or ribodoxo or doxolem or doxotec or fauldoxo or farmiblastina or adrim or doxil or rubex))
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. TS=(animal or animals or mice or mouse or rat or rats or hamster* or dog or dogs or cat or cats or rabbit* or sheep or bovine)
13. 11 not 12

Cochrane Central Register of Controlled Trials (CENTRAL)

The Cochrane Library Issue 1, 2004
Accessed via http://www.nelh.nhs.uk/cochrane.asp
Search date: 15 April 2004

#1 retinoblastoma
#2 retinoblastoma single term (MeSH)
#3 retinal neoplasms single term (MeSH)
#4 ((retina* near neoplasm*) or (retina* near cancer*) or (retina* near tumor*) or (retina* near tumour*) or (retina* near malignan*) or (retina* near carcinoma*) or (retina* near adenocarcinoma*) or (retina* near sarcoma*))
#5 #1 or #2 or #3 or #4

BIOSIS

1969 to April week 2 2004
Accessed via Dialog (file 5)
Search date: 22 April 2004

B 5
1. S retinoblastoma/ti,ab
2. S ((retina or retinal) (w2) (cancer or cancers or cancerous))/ti,ab
3. S ((retina or retinal) (w2) (neoplasm or neoplasms)/ti,ab
4. S ((retina or retinal) (w2) (tumor or tumors or tumour or tumours))/ti,ab
5. S ((retina or retinal) (w2) (malignancy or malignancies))/ti,ab
6. S ((retina or retinal) (w2) (carcinoma or carcinomas)/ti,ab
7. S ((retina or retinal) (w2) (adenocarcinoma or adenocarcinomas)/ti,ab
8. S ((retina or retinal) (w2) (sarcoma or sarcomas)/ti,ab
9. S s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8
10. S (enucleation or enucleated or enucleating or exenterat? or eviscerat?)/ti,ab
11. S ((eye or eyes or eyeball? or eye()ball or globe or globes or orbit or orbits) (w2) (removal or remove or removes or removing or extract or extracts or extraction))/ti,ab
12. S (brachytherapy or brachytherapies)/ti,ab
13. S (radiotherapy or radiotherapies or radiotherapeutic or radiotherapeutics)/ti,ab
14. S (curietherapy or cryotherapy or cryosurgery or cryocoagulation)/ti,ab
15. S (cold(w) (therapy or therapies))/ti,ab
16. S ((laser or lasers or light) (w) coagulation))/ti,ab
17. S (photocoagulation or phototherapy or phototherapeutic? or thermocoagulation or photoablation)/ti,ab
18. S (radiation or irradiation or irradiate or irradiates or irradiated or re()irradiate or re()irradiated or re()irradiation)/ti,ab
19. S plaque/ti,ab
20. S (hyperthermia or thermotherapy or fever(w)therapy or fever(w)therapies)/ti,ab
21. S (chemotherapy or chemotherapies or chemotherapeutic)/ti,ab
22. S (chemothermotherapy or thermochemotherapy or chemoreduction or chemoprophylaxis)/ti,ab
23. S (laser (w) (therapy or therapies))/ti,ab
24. S surgery/ti,ab
25. S (photodynamic (w) therapy or therapies))/ti,ab
26. S (carboplatin or vincristine or etoposide or cyclophosphamide or cisplatin)/ti,ab
27. S (ciclosporin? or cyclosporin? or idarubicin or doxorubicin or adramycin)/ti,ab

28. S (carbosol or paraplatin or carbosin or carboplat or ribocardo or blastocarb or carbotec or displata or novoplat or nealorin or novoplatinum or ercar or paraplatin or platinwas or kemocarb)/ti,ab
29. S (oncovin or vincrin or cellcristin or farmistin or citomid or filcrin or vincasar or vintec or faulcris or pericristine or vincrisul)/ti,ab
30. S (abiposid or cehaposid or exitop or vepesid or etopophos or eposid or etopofos or celltop or eto cs or eto-gry or etomedac or riboposid or lastet or etopos or kenazol or lastet or seroposide or vp-tec or eposin or fytosid or toposar)/ti,ab
31. S (endoxan or cycloblastin or cycloblastine or enduxan or genuxal or cytoxan or procytox or caroloxan or sendoxan or cytophosphan or fosfaseron or genoxal or ledoxina or sendoxan or alkyloxan or endoxana or neosar)/ti,ab
32. S (abiplatin or platiblastin or platinol or platistine or cisplatyl or platiran or citosin or lederplatin or platinex or platosin or citoplatino or platamine or blastolem or niyaplat or plastistil or seroplatin or tecnoplatin or tisplal or platistin or faulplatin or neoplatin or placis or platistil or abiplatin or kemoplat)/ti,ab
33. S (sandimmun or neoral or neural-sandimmun or colosina or immulem or consupren or gengraf)/ti,ab
34. S (zavedos or idamycin)/ti,ab
35. S (adriamycin or myocet or adriblastin or caelyx or doxorubin or adriblastina or rubex or adriblastine or adrimedac or doxo-cell or ribodoxo or doxolem or doxotec or fauldoxo or farmiblastina or adrim or doxil or rubex)/ti,ab
36. S s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20
37. S s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30
38. S s31 or s32 or s33 or s34 or s35
39. S s36 or s37 or s38
40. S s9 and s39
41. S animals/de
42. S s40 not s41

Pascal

1973 to April week 2 2004
Accessed via Dialog (file 144)
Search date: 22.4.05

B 144
1. S retinoblastoma/ti,ab
2. S ((retina or retinal) (w2) (cancer or cancers or cancerous))/ti,ab
3. S ((retina or retinal) (w2) (neoplasm or neoplasms)/ti,ab
4. S ((retina or retinal) (w2) (tumor or tumors or tumour or tumours))/ti,ab
5. S ((retina or retinal) (w2) (malignancy or malignancies))/ti,ab
6. S ((retina or retinal) (w2) (carcinoma or carcinomas)/ti,ab
7. S ((retina or retinal) (w2) (adenocarcinoma or adenocarcinomas)/ti,ab
8. S ((retina or retinal) (w2) (sarcoma or sarcomas)/ti,ab
9. S s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8
10. S (enucleation or enucleated or enucleating or exenterat? or eviscerat?)/ti,ab
11. S ((eye or eyes or eyeball? or eye()ball or globe or globes or orbit or orbits) (w2) (removal or remove or removes or removing or extract or extracts or extraction))/ti,ab
12. S (brachytherapy or brachytherapies)/ti,ab
13. S (radiotherapy or radiotherapies or radiotherapeutic or radiotherapeutics)/ti,ab
14. S (curietherapy or cryotherapy or cryosurgery or cryocoagulation)/ti,ab
15. S (cold(w) (therapy or therapies))/ti,ab
16. S ((laser or lasers or light) (w) coagulation))/ti,ab
17. S (photocoagulation or phototherapy or phototherapeutic? or thermocoagulation or photoablation)/ti,ab
18. S (radiation or irradiation or irradiate or irradiates or irradiated or re()irradiate or re()irradiated or re()irradiation)/ti,ab
19. S plaque/ti,ab
20. S (hyperthermia or thermotherapy or fever(w)therapy or fever(w)therapies)/ti,ab
21. S (chemotherapy or chemotherapies or chemotherapeutic)/ti,ab
22. S (chemothermotherapy or thermochemotherapy or chemoreduction or chemoprophylaxis)/ti,ab
23. S (laser (w) (therapy or therapies))/ti,ab
24. S surgery/ti,ab
25. S (photodynamic (w) therapy or therapies))/ti,ab
26. S (carboplatin or vincristine or etoposide or cyclophosphamide or cisplatin)/ti,ab
27. S (ciclosporin? or cyclosporin? or idarubicin or doxorubicin or adramycin)/ti,ab
28. S (carbosol or paraplatin or carbosin or carboplat or ribocardo or blastocarb or carbotec or displata or novoplat or nealorin or novoplatinum or ercar or paraplatin or platinwas or kemocarb)/ti,ab
29. S (oncovin or vincrin or cellcristin or farmistin

or citomid or filcrin or vincasar or vintec or faulcris or pericristine or vincrisul)/ti,ab
30. S (abiposid or cehaposid or exitop or vepesid or etopophos or eposid or etopofos or celltop or eto cs or eto-gry or etomedac or riboposid or lastet or etopos or kenazol or lastet or seroposide or vp-tec or eposin or fytosid or toposar)/ti,ab
31. S (endoxan or cycloblastin or cycloblastine or enduxan or genuxal or cytoxan or procytox or caroloxan or sendoxan or cytophosphan or fosfaseron or genoxal or ledoxina or sendoxan or alkyloxan or endoxana or neosar)/ti,ab
32. S (abiplatin or platiblastin or platinol or platistine or cisplatyl or platiran or citosin or lederplatin or platinex or platosin or citoplatino or platamine or blastolem or niyaplat or plastistil or seroplatin or tecnoplatin or tisplal or platistin or faulplatin or neoplatin or placis or platistil or abiplatin or kemoplat)/ti,ab
33. S (sandimmun or neoral or neural-sandimmun or colosina or immulem or consupren or gengraf)/ti,ab
34. S (zavedos or idamycin)/ti,ab
35. S (adriamycin or myocet or adriblastin or caelyx or doxorubin or adriblastina or rubex or adriblastine or adrimedac or doxo-cell or ribodoxo or doxolem or doxotec or fauldoxo or farmiblastina or adrim or doxil or rubex)/ti,ab
36. S s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20
37. S s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30
38. S s31 or s32 or s33 or s34 or s35
39. S s36 or s37 or s38
40. S s9 and s39
41. S animals/DE
42. S s40 not s41

Dissertation Abstracts

1861 to March 2004
Accessed via Dialog (file 65)
Search date: 21 April 04

B 35
1. S retinoblastoma/ti,ab
2. S ((retina or retinal) (w2) (cancer or cancers or cancerous))/ti,ab
3. S ((retina or retinal) (w2) (neoplasm or neoplasms)/ti,ab
4. S ((retina or retinal) (w2) (tumor or tumors or tumour or tumours))/ti,ab
5. S ((retina or retinal) (w2) (malignancy or malignancies))/ti,ab
6. S ((retina or retinal) (w2) (carcinoma or carcinomas)/ti,ab
7. S ((retina or retinal) (w2) (adenocarcinoma or adenocarcinomas)/ti,ab
8. S ((retina or retinal) (w2) (sarcoma or sarcomas)/ti,ab
9. S s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8
10. S (enucleation or enucleated or enucleating or exenterat? or eviscerat?)/ti,ab
11. S ((eye or eyes or eyeball? or eye()ball or globe or globes or orbit or orbits) (w2) (removal or remove or removes or removing or extract or extracts or extraction))/ti,ab
12. S (brachytherapy or brachytherapies)/ti,ab
13. S (radiotherapy or radiotherapies or radiotherapeutic or radiotherapeutics)/ti,ab
14. S (curietherapy or cryotherapy or cryosurgery or cryocoagulation)/ti,ab
15. S (cold(w) (therapy or therapies))/ti,ab
16. S ((laser or lasers or light) (w) coagulation))/ti,ab
17. S (photocoagulation or phototherapy or phototherapeutic? or thermocoagulation or photoablation)/ti,ab
18. S (radiation or irradiation or irradiate or irradiates or irradiated or re()irradiate or re()irradiated or re()irradiation)/ti,ab
19. S plaque/ti,ab
20. S (hyperthermia or thermotherapy or fever(w)therapy or fever(w)therapies)/ti,ab
21. S(chemotherapy or chemotherapies or chemotherapeutic)/ti,ab
22. S (chemothermotherapy or thermochemotherapy or chemoreduction or chemoprophylaxis)/ti,ab
23. S (laser (w) (therapy or therapies))/ti,ab
24. S surgery/ti,ab
25. S (photodynamic (w) therapy or therapies))/ti,ab
26. S (carboplatin or vincristine or etoposide or cyclophosphamide or cisplatin)/ti,ab
27. S (ciclosporin? or cyclosporin? or idarubicin or doxorubicin or adramycin)/ti,ab
28. S (carbosol or paraplatin or carbosin or carboplat or ribocardo or blastocarb or carbotec or displata or novoplat or nealorin or novoplatinum or ercar or paraplatin or platinwas or kemocarb)/ti,ab
29. S (oncovin or vincrin or cellcristin or farmistin or citomid or filcrin or vincasar or vintec or faulcris or pericristine or vincrisul)/ti,ab
30. S (abiposid or cehaposid or exitop or vepesid or etopophos or eposid or etopofos or celltop or eto cs or eto-gry or etomedac or riboposid or lastet or etopos or kenazol or lastet or seroposide or vp-tec or eposin or fytosid or toposar)/ti,ab

31. S (endoxan or cycloblastin or cycloblastine or enduxan or genuxal or cytoxan or procytox or caroloxan or sendoxan or cytophosphan or fosfaseron or genoxal or ledoxina or sendoxan or alkyloxan or endoxana or neosar)/ti,ab
32. S (abiplatin or platiblastin or platinol or platistine or cisplatyl or platiran or citosin or lederplatin or platinex or platosin or citoplatino or platamine or blastolem or niyaplat or plastistil or seroplatin or tecnoplatin or tisplal or platistin or faulplatin or neoplatin or placis or platistil or abiplatin or kemoplat)/ti,ab
33. S (sandimmun or neoral or neural-sandimmun or colosina or immulem or consupren or gengraf)/ti,ab
34. S (zavedos or idamycin)/ti,ab
35. S (adriamycin or myocet or adriblastin or caelyx or doxorubin or adriblastina or rubex or adriblastine or adrimedac or doxo-cell or ribodoxo or doxolem or doxotec or fauldoxo or farmiblastina or adrim or doxil or rubex)/ti,ab
36. S s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20
37. S s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30
38. S s31 or s32 or s33 or s34 or s35
39. S s36 or s37 or s38
40. S s9 and s39

Inside conferences

1993 to April week 3 2004
Accessed via Dialog (file 65)
Search date: 21 April 04

B 65

1. S retinoblastoma/ti,ab
2. S ((retina or retinal) (w2) (cancer or cancers or cancerous))/ti,ab
3. S ((retina or retinal) (w2) (neoplasm or neoplasms)/ti,ab
4. S ((retina or retinal) (w2) (tumor or tumors or tumour or tumours))/ti,ab
5. S ((retina or retinal) (w2) (malignancy or malignancies))/ti,ab
6. S ((retina or retinal) (w2) (carcinoma or carcinomas)/ti,ab
7. S ((retina or retinal) (w2) (adenocarcinoma or adenocarcinomas)/ti,ab
8. S ((retina or retinal) (w2) (sarcoma or sarcomas)/ti,ab
9. S s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8
10. S (enucleation or enucleated or enucleating or exenterat? or eviscerat?)/ti,ab
11. S ((eye or eyes or eyeball? or eye()ball or globe or globes or orbit or orbits) (w2) (removal or remove or removes or removing or extract or extracts or extraction))/ti,ab
12. S (brachytherapy or brachytherapies)/ti,ab
13. S (radiotherapy or radiotherapies or radiotherapeutic or radiotherapeutics)/ti,ab
14. S (curietherapy or cryotherapy or cryosurgery or cryocoagulation)/ti,ab
15. S (cold(w) (therapy or therapies))/ti,ab
16. S ((laser or lasers or light) (w) coagulation))/ti,ab
17. S (photocoagulation or phototherapy or phototherapeutic? or thermocoagulation or photoablation)/ti,ab
18. S (radiation or irradiation or irradiate or irradiates or irradiated or re()irradiate or re()irradiated or re()irradiation)/ti,ab
19. S plaque/ti,ab
20. S (hyperthermia or thermotherapy or fever(w)therapy or fever(w)therapies)/ti,ab
21. S (chemotherapy or chemotherapies or chemotherapeutic)/ti,ab
22. S (chemothermotherapy or thermochemotherapy or chemoreduction or chemoprophylaxis)/ti,ab
23. S (laser (w) (therapy or therapies))/ti,ab
24. S surgery/ti,ab
25. S (photodynamic (w) therapy or therapies))/ti,ab
26. S (carboplatin or vincristine or etoposide or cyclophosphamide or cisplatin)/ti,ab
27. S (ciclosporin? or cyclosporin? or idarubicin or doxorubicin or adramycin)/ti,ab
28. S (carbosol or paraplatin or carbosin or carboplat or ribocardo or blastocarb or carbotec or displata or novoplat or nealorin or novoplatinum or ercar or paraplatin or platinwas or kemocarb)/ti,ab
29. S (oncovin or vincrin or cellcristin or farmistin or citomid or filcrin or vincasar or vintec or faulcris or pericristine or vincrisul)/ti,ab
30. S (abiposid or cehaposid or exitop or vepesid or etopophos or eposid or etopofos or celltop or eto cs or eto-gry or etomedac or riboposid or lastet or etopos or kenazol or lastet or seroposide or vp-tec or eposin or fytosid or toposar)/ti,ab
31. S (endoxan or cycloblastin or cycloblastine or enduxan or genuxal or cytoxan or procytox or caroloxan or sendoxan or cytophosphan or fosfaseron or genoxal or ledoxina or sendoxan or alkyloxan or endoxana or neosar)/ti,ab
32. S (abiplatin or platiblastin or platinol or platistine or cisplatyl or platiran or citosin or lederplatin or platinex or platosin or citoplatino or platamine or blastolem or niyaplat or plastistil or seroplatin or tecnoplatin or tisplal

or platistin or faulplatin or neoplatin or placis or platistil or abiplatin or kemoplat)/ti,ab
33. S (sandimmun or neoral or neural-sandimmun or colosina or immulem or consupren or gengraf)/ti,ab
34. S (zavedos or idamycin)/ti,ab
35. S (adriamycin or myocet or adriblastin or caelyx or doxorubin or adriblastina or rubex or adriblastine or adrimedac or doxo-cell or ribodoxo or doxolem or doxotec or fauldoxo or farmiblastina or adrim or doxil or rubex)/ti,ab
36. S s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20
37. S s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30
38. S s31 or s32 or s33 or s34 or s35
39. S s36 or s37 or s38
40. S s9 and s39

SIGLE

1980 to December 2003
Accessed via Ovid webSPIRS
http://arc.uk.ovid.com/wespirs
Search date: 15 April 2004

#1 retinoblastoma
#2 (retina* near2 (cancer* or neoplasm* or tumo?r* or malignan* or carcinoma* or adenocarcinoma* or sarcoma*))
#1 or #2

Lilacs

1982 to 12 April 2004
Accessed via the BVS Virtual Health Library
http://bases.bireme.br
Search date: 16 April 2004

Each line searched and results saved:

enucleat$ or eviscerat$ and retinoblastoma
brachytherap$ or curietherap$ and retinoblastoma
radiotherap$ or cryotherap$ and retinoblastoma
"cold therap$" or cryosurg$ and retinoblastoma
cryocoagulat$ or coagulat$ and retinoblastoma
photocoagulat$ or photoablat$ and retinoblastoma
phototherap$ or thermocoagulat$ and retinoblastoma
radiation or irradiat$ and retinoblastoma
reirradiat$ or plaque$ and retinoblastoma
hypertherm$ or "fever herap$" and retinoblastoma
thermotherap$ or chemotherap$ and retinoblastoma
"antineoplastic combined chemotherapy protocols" or "combined modality therapy" and retinoblastoma
chemotheramatherap$ or themochemotherap$ and retinoblastoma
chemoreduction or chemoprophylaxis and retinoblastoma
photodynamic or surgery and retinoblastoma
laser or carboplatin and retinoblastoma
vincristine or etoposide and retinoblastoma
cyclophosphamide or cisplatin and retinoblastoma
ciclosporin$ or cyclosporin$ and retinoblastoma
idarubicin or doxorubicin and retinoblastoma

ICRP

2000 to 2004
Accessed via http://www.cancerportfolio.org
Search date: 23 April 2004

Each of the following terms was searched for:

Retinoblastoma
Retina* $neoplasm
Retina* $cancer
Retina* $tumor
Retina* $tumour
Retina* $malignancy
Retina* $carcinoma
Retina* $adenocarcinoma
Retina* $sarcoma

Current Controlled Trials

Accessed via www.controlled-trials,com/mrct/search
Search date: 23 April 2004

Each of the following terms was searched for:

retinoblastoma
Retina% and neoplasm%
Retina% and cancer%
Retina% and tumor%
Retina% and tumour%
Retina% and maligan%
Retina% and carcinoma%
Retina% and adenocarinoma%
Retina% and sarcoma%

National Cancer Institute Clinical Trials PDQ

Accessed via http://cancer.gov/clinicaltrials
Search date: 23 April 2004

Type of cancer = retinoblastoma
Type of trial = all

NRR

Issue 1, 2004
Accessed via CD-RoM
Search date: 15 April 2004

1. Retinoblastoma:ME
2. Retinal-neoplasms:ME
3. retinoblastoma
4. (((((((Retina* near neoplasm*) or (retina* near cancer*)) OR (retina* near Carcinaoma*)) OR (retina* near malignan*)) OR (retina* near tumor*)) OR (Retina* near tumour*)) OR (retina* near adenocarcinoma*)) OR (retina* near sarcoma*))
5. ((#1 or #2) or #3) or 4)

NTIS, US Department of Commerce

1990 to 2004
Accessed via www.ntis.gov
Search date: 23 April 2004

Each of the following terms was searched for:

Retinoblastoma
Retina and neoplasm
Retina and cancer
Retina and tumor
Retina and tumour
Retina and malignancy
Retina and carcinoma
Retina and adenocarcinoma
Retina and sarcoma

Greylit Network

1974 to 2004
Accessed via http://graylit.osti.gov
Search date: 23 April 2004

Each of the following search terms was searched for:

Retinoblastoma
Retina* and neoplasm*
Retina* and cancer*
Retina* and tumor*
Retina* and tumour*
Retina* and malignan*
Retina* and carcinoma*
Retina* and adenocarcinoma*
Retina* and sarcoma*

OMNI

Accessed via http://omni.ac.uk
Search date: 23 April 2004

Retinoblastoma
Retina* and neoplasm*
Retina* and cancer*
Retina* and tumor*
Retina* and tumour*
Retina* and malignan*
Retina* and carcinoma*
Retina* and adenocarcinoma*
Retina* and sarcoma*

Google

Accessed via http://www.google
Search date: 23 April 2004

Each of the following terms was searched for:

Search all the words:
retinoblastoma enucleation
retinoblastoma evisceration
retinoblastoma brachytherapy
retinoblastoma radiotherapy
retinoblastoma cryotherapy
retinoblastoma cryosurgery
retinoblastoma coagulation
retinoblastoma phototherapy
retinoblastoma radiation
retinoblastoma plaque
retinoblastoma chemotherapy
retinoblastoma surgery
retinoblastoma laser
retinoblastoma carboplatin
retinoblastoma vincristine
retinoblastoma etoposide
retinoblastoma cyclophosphamide
retinoblastoma cisplatin
retinoblastoma ciclosporin
Retinoblastoma cyclosporin
Retinoblastoma iadrubicin
Retinoblastoma doxorubicin

Appendix 4

Criteria used to assess the methodological quality of included studies

TABLE 18 *Methodological criteria*

Was the method of assignment of patients to interventions described? (A description of the method of assignment was also extracted)
Attempt to balance groups by design?
Were relevant prognostic variables identified?[a]
Were patients matched for relevant prognostic/confounding variables or the effect of any difference evaluated in valid statistical analyses?
Were the intervention groups comparable at baseline?
Was the number of patients lost to follow-up reported? Were the rates similar across groups?
Was the follow-up period, range and mean reported?
Do the analyses adjust for different lengths of follow-up for patients?
Was the follow-up long enough for the outcomes to occur?
Was the treatment clearly specified?
Were there clearly defined criteria for measuring outcomes?

[a] Relevant prognostic variables included RE or other staging classification, unilateral or bilateral disease, recurrent disease or first presentation, and previous treatments.

Appendix 5

Results of quality assessment

TABLE 19

Study	Description of assignment to interventions	Groups balanced by design	Identification of relevant prognostic variables	Patients were matched for relevant prognostic/ confounding variables or effect of any difference was evaluated in valid statistical analyses	Intervention groups comparable at baseline	Number of patients lost to follow-up was reported, and rates were similar across groups	Follow-up period, range and mean reported	Analyses adjust for different lengths of follow-up	Follow-up long enough for the outcomes to occur?	Treatment clearly specified	Clearly defined criteria for measuring outcomes
Akiyama *et al.*, 1989[132]	×	×	✓	×	NR	NR	×	×	NR	×	×[a]
Amendola *et al.*, 1990[122]	×	×	✓	×	NR	NR	✓	×	NR	✓	×
Amendola *et al.*, 1989[123]	✓	×	✓	×	×	NR	✓	×	×	×	×
Antoneli *et al.*, 2003[130]	✓	×	✓	×	✓	NR[b]	✓[b]	✓	✓	✓	✓
Blach *et al.*, 1996[128]	✓	×	✓	✓	✓	NA	✓	✓	✓	✓	✓
Cassady *et al.*, 1969[109]	×	×	✓	×	NR	NR	×	×	NR	×	×
Draper *et al.*, 1986[126]	×	×	×	×	NR	NA	NR	✓	✓	×	×
Foote *et al.*, 1989[113]	✓	×	✓	×	NR	NR	✓[b]	×	✓	✓	×
Guenduez *et al.*, 1998[134]	✓	×	✓	✓	✓	×	✓[b]	×	×	✓[c]	✓
Hadjistilianou *et al.*, 1991[108]	×	×	✓	NR	×	✓	×	×	✓	×	✓
Hauffa *et al.*, 1995[125]	×	×	×	×	NR	NA	✓	✓	×	✓	✓
Haye *et al.*, 1989[127]	✓	×	✓	×	NR	×	×	×	✓	×	×
Honavar *et al.*, 2002[38]	✓	×	✓	✓	×	NA	✓	✓	✓	✓	✓
Hungerford *et al.*, 1997[124]	✓	×	✓	×	NR	NA	✓	×	✓	×	×
Hungerford *et al.*, 2004[106]	×	×	✓	×	NR	×	✓	×	✓	×	×
Kaste *et al.*, 1997[114]	×	×	×	×	NR	NA	✓[b]	×	✓	×	✓
Lee *et al.*, 2003[129]	✓	×	×	×	NR	NR	✓[b]	×[d]	×	×[e]	NR[f]
Lee *et al.*, 2000[116]	✓	×	✓	✓	NR	NR[b]	✓	×	✓	×	×
Merrill *et al.*, 1996[110]	×	×	×	×	NR	NR	×	×	NR	✓	✓
Messmer *et al.*, 1990[112]	×	×	×	×	NR	NR	✓[b]	✓[g]	✓	×	✓
Mohr *et al.*, 1990[120]	×	×	×	×	NR	×	×	×	✓	✓	NR
Moll *et al.*, 2001[117]	×	×	×	×	NR	✓[b]	✓	✓	✓	NR[h]	✓
Pasqualini *et al.*, 1991[119]	×	×	×	×	NR	NA	✓	×	✓	✓	✓
Roarty *et al.*, 1988[115]	×	×	×	×	NR	NR	✓	✓	✓	×	NR
Scott *et al.*, 1999[121]	✓	×	✓	×	✓	NR	✓	✓	✓	✓	✓[i]

continued

TABLE 19 (cont'd)

Study	Description of assignment to interventions	Groups balanced by design	Identification of relevant prognostic variables	Patients were matched for relevant prognostic/ confounding variables or effect of any difference was evaluated in valid statistical analyses	Intervention groups comparable at baseline	Number of patients lost to follow-up was reported, and rates were similar across groups	Follow-up period, range and mean reported	Analyses adjust for different lengths of follow-up	Follow-up long enough for the outcomes to occur?	Treatment clearly specified	Clearly defined criteria for measuring outcomes
Shields *et al.*, 1997[133]	✓	×	✓	×	NR	✓	✓[b]	×	×	×[j]	×
Shields *et al.*, 2001[131]	✓	×	✓	×	×	NR	✓	×	×	×	✓
Srivastava *et al.*, 1984[118]	×	×	✓	×	NR	NR[b]	×[k]	×	×	×	×[l]
Sussman *et al.*, 2003[111]	✓	×	✓	×	×	NA	✓	×	✓	NR	✓
Wolff *et al.*, 1981[107]	NR[m]	✓[n]	✓	×[n]	NR	×[o]	✓	NR[p]	✓	✓	×[q]
Wong *et al.*, 1997[5]	×	✓/×[r]	✓	×[s]	NR	✓[b]	×[b]	✓	✓	×	✓

NR, not reported or unclear; NA, not applicable.
[a] No information was reported on how death was established in patients from the Japanese Registry.
[b] Overall value given for combined treatment groups, but not reported for each treatment group.
[c] Treatment was not clearly specified for patients receiving focal therapies.
[d] Analyses did not adjust for different lengths of follow-up for the treatment groups of interest to this review.
[e] Focal therapy and radiotherapy given are not clearly specified.
[f] The authors did not provide a clear definition of a new tumour.
[g] The authors state that there may be some bias with regard to different follow-up intervals in the analysis comparing two EBRT techniques because the numbers were too small to adjust for different follow-ups in the life tables.
[h] Only detailed for radiation treatment.
[i] The outcome measure was clearly defined, but the method of measurement was not given.
[j] Minimal information was given on adjuvant therapy.
[k] The authors only report the number of patients followed up within specific periods for each treatment group. The exact length of follow-up is not given.
[l] It is unclear whether the authors have measured disease-free survival or overall survival.
[m] The method of randomisation of randomly allocated patients is not given. No information is given on how non-randomised patients were allocated.
[n] Only RE group V were eligible for inclusion.
[o] Rates were reported for each group, but more patients were lost from regimen II.
[p] It is unclear whether Kaplan–Meier survival curves were used in the analysis.
[q] It is unclear how the authors investigated recurrence.
[r] The case–control study did balance the groups by design, but the cohort study did not.
[s] The effect of possible confounding variables was not considered for the two treatment groups in the cohort study. Relevant factors were partly controlled for in the case–control study.

Appendix 6

Data extraction tables for included studies

Publication details
Authors (year):
Akiyama *et al*. (1989)[132]
Country: Japan
Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To evaluate the treatment outcomes and side-effects associated with the use of chemotherapy in patients with retinoblastoma

Study design (brief details):
The treatment outcomes of patients who were treated with chemotherapy at Nagasaki University Hospital from 1979 to 1985 were compared with retinoblastoma patients registered between 1980 and 1981 in Japan who had not received chemotherapy

Retrospective/prospective:
The patients treated at a single clinic were studied prospectively, and the patients from the Japanese register were studied retrospectively

How patients were allocated to their treatment group:
Patients in the single clinic were allocated to treatment group according to hospital protocol. It is not stated how patients from the Japanese register were allocated treatment

Sample size calculations:
Not performed

Statistical analyses:
Not explicitly stated, although significance tests were performed

Analysis by eyes or participants:
Eyes and participants

Inclusion criteria:
For the comparison group participants registered in Japan in 1980 and 1981 had to meet the following criteria: clinical features of the affected eye were classified, histological findings of the enucleated eye were documented, 5-year post-therapy results were confirmed, and the tumour was limited to the eyeball

Retinoblastoma classification system used:
RE

Notes: The authors identified two further treatment groups. The four patients with bilateral disease from the single clinic were combined with bilateral cases selected from the register. Patients were compared based on whether they received treatment regimen I or II. Regimen I was defined as the early chemotherapy group where participants were treated with chemotherapy within 1 month after the initiation of conservative therapy, whereas regimen II was defined as the late or non-chemotherapy group, which included participants who were treated with chemotherapy more than 1 month following conservative therapy, or had not received chemotherapy. This did not meet the inclusion criteria and is not included in this review

Interventions
Treatment 1:
Chemotherapy consisting of vincristine and cyclophosphamide

Dose, number of treatments, etc.:
In most cases 1.5–2 mg of vincristine and 300 mg of cyclophosphamide per square metre of BSA delivered intravenously alternating every 2 weeks for 20 weeks or every week for 6 weeks, followed by 1–1.5 mg of vincristine and 200 mg of cyclophosphamide per square metre of BSA alternately every 2 weeks or every week for approximately 1 year (individual patient treatment regimens are reported)

continued

Period of treatment:
Approximately 1 year for 12 patients; 20 weeks for 1 patient; 1 year 20 weeks for 1 patient

Length of follow-up (mean, SD, range, etc.):
Not stated

Adjunctive treatments:
All patients with bilateral retinoblastoma also received xenon photocoagulation, cryosurgery and enucleation of the worse eye. Patients with unilateral retinoblastoma were enucleated initially

Treatment 2:
No patients had received chemotherapy. Regimen not specified

Dose, number of treatments, etc:
Not reported

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
At least 5 years

Adjunctive treatments:
Not specified, although other conservative treatments were administered

Participants:
Total number of participants allocated (for inclusion in the comparison of single clinic compared with register):
Total (*n*): 51
Patients from single clinic (*n*): 14
Patients from the register (*n*): 37

Number of eyes:
Total (*n*): 65 (58 used in comparison)
Treatment 1 (*n*): 18
Treatment 2 (*n*): 37

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported

Age of participants:
Total: not reported
Treatment 1: mean age at diagnosis 21.9 months (range 2–54 months); mean age at follow-up 5 years 11 months (range 2 years 5 month to 9 years 1 month)
Treatment 2: not reported

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral):
Total (*n*): 47 unilateral, 4 bilateral
Treatment 1 (*n*): 10 unilateral, 4 bilateral
Treatment 2 (*n*): 37 unilateral, 0 bilateral

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): group Ia = 2, group Ib = 2, group IIa = 2, group IIb = 2, group IIIa = 1, group IIIb = 3, group IVb = 4, group Va = 28, group Vb = 11

Treatment 1 (*n*): group Ia = 1, group IIa = 1, group IIb = 2, group IIIb = 1, group IVb = 1, group Va = 8, group Vb = 4

Treatment 2 (*n*): group Ia = 1, group Ib = 2, group IIa = 1, group IIIa = 1, group IIIb = 2, group IVa = 0, group IVb = 3, group Va = 20, group Vb = 7

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Other relevant baseline/tumour characteristics: Invasion of the choroid
Total (*n*): 2/51
Treatment 1 (*n*): 2/14
Treatment 2 (*n*): 0/37

continued

Results
Outcome 1
Description:
Survival (number of patients alive)

Treatment 1: 14/14
Treatment 2: 36/37

The authors state that they compared 30 patients from the register with group IV and V eyes with the clinic group and found that there was no significant difference

BSA, body surface area.

Publication details
Authors (year):
Amendola *et al.* (1990)[122]

Country: USA

Type of publication (full paper, abstract):
Full paper

Related publications:
Some patients evaluated in this study were also included in an additional study performed by Amendola *et al.*[123]

Study design
Authors' objective:
To review the effects of different radiotherapy techniques according to stage of intraocular involvement in patients with retinoblastoma

Study design (brief details):
The records of children who received radiotherapy (EBRT or brachytherapy) for the treatment of retinoblastoma at a single hospital with retinoblastoma from 1975 to 1988, or patients initially treated with enucleation or EBRT elsewhere and subsequently referred to the single hospital for consideration of further treatment during this period were reviewed to determine treatment outcome. Three treatment groups were subsequently identified: brachytherapy, EBRT and the referral group who initially received EBRT or enucleation and were given brachytherapy as salvage therapy

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not explicitly stated, although indications for plaque therapy were reported for treatment group 1

Sample size calculations:
Not performed

Statistical analyses:
No statistical comparisons between the treatment groups were performed. The number of patients with outcome of interest was reported

Analysis by eyes or participants:
Eyes and patients

Inclusion criteria:
Not reported

Retinoblastoma classification system used:
RE

Notes: Treatment group 3 consists of 27 patients (51 eyes) who were given initial treatment elsewhere and were subsequently referred to the single hospital that conducted the research for consideration of further treatment. The initial treatment consisted of enucleation of the eye with the most advanced form of disease and EBRT in the remaining eyes (16 eyes were enucleated and 35 eyes were given EBRT)
The salvage treatment given at the referral hospital was brachytherapy (29/35 non-enucleated eyes) for patients with recurrent retinoblastoma or as a treatment 'boost'. The authors do not report the salvage treatment given, if any, to the remaining 6/35 eyes initially treated with EBRT
The outcomes for this treatment group are presented only for the 29 eyes initially treated with EBRT and subsequently given brachytherapy as salvage therapy

continued

Interventions
Treatment 1:
Brachytherapy (^{60}Co, ^{125}I, ^{192}Ir, or ^{106}Ru)

Dose, number of treatments, etc.:
Brachytherapy using ^{60}Co, ^{125}I, ^{192}Ir or ^{106}Ru radioactive plaques. The dosage delivered was 40 Gy to the midglobe and 100–120 Gy to the sclera

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
5–115 months (median 38 months)

Adjunctive treatments:
None (patients with bilateral retinoblastoma had the contralateral eye treated by enucleation or EBRT)

Treatment 2:
EBRT

Dose, number of treatments, etc.:
Radiation was delivered using a 6-MeV linear accelerator with field sizes from 4 × 4 cm to 5 × 6 cm in dimension. The technique involved anterior and lateral wedged pairs, bilateral opposed portals, or a lateral portal alone
Radiation dose ranged from 40 to 45 Gy delivered in daily fractions of 1.5–2 Gy

Period of treatment:
4–5.5 weeks. Treatment was given on 5 days per week and all fields were treated daily

Length of follow-up (mean, SD, range, etc.):
5–93 months (median 35 months)

Adjunctive treatments:
None (patients with bilateral retinoblastoma had the contralateral eye treated by enucleation or EBRT)

Treatment 3:
EBRT plus brachytherapy. This group consists of 27 patients (51 eyes) who were given initial treatment elsewhere and were subsequently referred to the single hospital that conducted the research for consideration of further treatment. The initial treatment given consisted of enucleation of the eye with the most advanced form of disease (16/51 eyes) and EBRT in the remaining eyes (35/51)
The salvage treatment given at the referral hospital was brachytherapy (29/35 non-enucleated eyes) for patients with recurrent retinoblastoma or as a treatment 'boost' to arrest the progression of disease. The authors do not report the salvage treatment given, if any, to the remaining 6/35 eyes initially treated with EBRT
The outcomes for this treatment group are presented only for the 29 eyes initially treated with EBRT subsequently given brachytherapy as salvage treatment

Dose, number of treatments, etc.:
Initial treatment with EBRT was given elsewhere using various field arrangements including D-shaped lateral portal, bilateral opposed portals, anterior electron beam and wedged pairs (anterior and lateral). Radiation doses ranged from 35 to 45 Gy delivered in daily fractions ranging from 1.5 to 3.5 Gy. ^{60}Co plaques and 4–6-meV irradiation were used
Salvage brachytherapy was given using ^{60}Co, ^{125}I, or ^{192}Ir. Doses delivered ranged from 40 Gy at the midglobe to 100 Gy at the sclera base where the plaque was attached
Multiple plaque insertion was used in patients with advanced disease delivered using sequential paired opposing plaques located on the equator of the globe and sutured to the sclera

Period of treatment:
Not stated

Length of follow-up (mean, SD, range, etc.):
6–126 months (median 49 months)

Adjunctive treatments:
Not stated

Participants
Number of participants allocated:
Total (*n*): 63
Treatment 1 (*n*): 24
Treatment 2 (*n*): 12
Treatment 3 (*n*): 27

continued

Number of eyes:
Total (*n*): 67
Treatment 1 (*n*): 25
Treatment 2 (*n*): 13
Treatment 3 (*n*): 29

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported
Treatment 1 (*n*): Not reported
Treatment 2 (*n*): Not reported
Treatment 3 (*n*): 2 patients were lost to follow-up

Age of participants:
Total: birth to 5 years (mean 12.5 months)
Treatment 1: mean 10.5 months
Treatment 2: mean 13.2 months
Treatment 3: mean 12.1 months

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 14 unilateral, 49 bilateral
Treatment 1 (*n*): 8 unilateral, 16 bilateral
Treatment 2 (*n*): 3 unilateral, 9 bilateral
Treatment 3 (*n*): 3 unilateral, 24 bilateral

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): group Ia = 4, group IIa = 17, group IIb = 2, group IIIa = 6, group IIIb = 1, group IVa = 3, group V = 23, group Va = 2, group Vb = 3
Treatment 1 (*n*): group Ia = 2, group IIa = 15, group IIIa = 4 eyes, group IVa = 1, group Va = 2, group Vb = 1
Treatment 2 (*n*): group IIa = 2, group IIb = 2, group IIIa = 2, group IVa = 2, group Vb = 3
Treatment 3 (*n*): group IIIb = 1, group V = 28

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results

Outcome 1
Description:
Treatment success defined as the number of eyes with NED at follow-up

Treatment 1: 22/25 (88%)
Treatment 2: 11/13 (85%)[a]
Treatment 3: 15/29 (52%)

[a] The abstract states that 77% of 13 eyes have NED, but the text states that 11 eyes have NED

Outcome 2
Description:
The number of eyes retained that developed a cataract (number of eyes that developed a cataract/number of eyes that were not enucleated)

Treatment 1: 2/22 (10%)[a]
Treatment 2: 5/11 (45%)[b]
Treatment 3: 9/15[c]

[a] 3/25 eyes were enucleated
[b] 2/13 eyes were enucleated
[c] 14 eyes were enucleated

continued

Outcome 4
Description
The number of eyes requiring additional treatment and the treatment given

Treatment 1: 7/25 (28%), three enucleated (two group Va and 1 group IIa), three brachytherapy (RE group not specified), one photocoagulation (RE group not specified).[a]
Treatment 2: 2/13 (15%), two enucleated (1 group IVa and 1 group Vb)
Treatment 3: 14/29 (48%), 14 enucleated (group not specified, although the majority of patients in this group had a severe form of disease and were of group V)

[a] The eyes that were given additional treatment with brachytherapy or photocoagulation were for new tumours that occurred in areas remote from the original plaque insertion

Outcome 5
Description:
Development of second tumours

Treatment 1: 0/24
Treatment 2: 0/12
Treatment 3: 4/29 (two primary bone tumours and two pineal tumours)

Outcome 6
Description:
Other adverse events (number of patients and type of adverse event)

Treatment 1: death: 0 patients; secondary tumours: 0
Treatment 2: death: 0 patients; secondary tumours: 0
Treatment 3: one dense lens opacification and phthisis of the eye, one moderate optic nerve atrophy, three neovascular glaucoma, four vitreous haemorrhage, one death. The authors report that all patients in this treatment group had bone growth abnormalities manifested as hypoplasia of the orbit, including sunken orbits in patients that received more than one dose of EBRT

NED, no evidence of disease.

Publication details
Authors (year):
Amendola *et al.* (1989)[123]

Country: USA

Type of publication (full paper, abstract):
Full paper

Related publications:
The patients evaluated in this study were also included in an additional study performed by Amendola *et al*.[122]

Study design
Authors' objective:
To examine the use of scleral plaque brachytherapy used in the treatment of retinoblastoma

Study design (brief details):
The treatment results of patients with retinoblastoma treated at the Hahenemann University Hospital or the Wills Eye Hospital between 1975 and 1986 were reviewed. Treatment with brachytherapy alone was compared with brachytherapy in conjunction with EBRT

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Patients were allocated to brachytherapy treatment only, on the basis of tumour size and location. The criteria used were small solitary tumours (RE groups I–IIIA) located anterior or posterior to the equator at least 3 mm from the optic nerve and small tumours with focal localised vitreous seeding and therefore not eligible for cryo- or photocoagulation Brachytherapy was given to patients who had had EBRT where the tumours had failed to regress within 2 months of completing EBRT or who had recurrent localised tumour

continued

Sample size calculations:
Not performed

Statistical analyses:
No formal statistical analyses were performed. The number of patients with relevant outcomes was reported

Analysis by eyes or participants:
Participants

Inclusion criteria:
Patients with retinoblastoma treated with brachytherapy between 1975 and 1986 by the Radiation Department of the Hahenemann University Hospital and the Wills Eye Hospital were eligible for inclusion

Retinoblastoma classification system used:
RE

Interventions
Treatment 1:
Brachytherapy (^{125}I, ^{192}Ir, ^{60}Co or ^{106}Ru)

Dose, number of treatments, etc.:
Brachytherapy using ^{125}I, ^{192}Ir, ^{60}Co or ^{106}Ru radioactive plaques. Radiation was delivered at approximately 40 Gy to the tumour apex and 100–200 Gy to the tumour base. The choice of plaque used was determined by the thickness of the tumour

Period of treatment:
Usually 48–72 hours

Length of follow-up (mean, SD, range, etc.):
Mean 3.4 years (median 2.5 years; range 8 months to 10 years)

Adjunctive treatments:
8/10 of the bilateral patients had enucleation of the more advanced eye with brachytherapy of the contralateral eye and 2/10 had cryotherapy of the less involved eye and brachytherapy of the more advanced eye

Note: Three patients were replaqued owing to pressure of the viable tumour on the short-term follow-up

Treatment 2:
EBRT and brachytherapy

Dose, number of treatments, etc:
Brachytherapy using ^{125}I, ^{192}Ir, or ^{60}Co radioactive plaques. Radiation was delivered at approximately 40 Gy to the tumour apex and 100–200 Gy to the tumour base. The choice of plaque used was determined by the thickness of the tumour. No details were provided for EBRT

Period of treatment:
Usually 48–72 hours for brachytherapy

Length of follow-up (mean, SD, range, etc.):
Mean 3.6 years (median 2 years; range 8 months to 10 years)

Adjunctive treatments:
15/15 bilateral patients received enucleation of the more advanced eye and EBRT and brachytherapy of the remaining eye

Note: Three patients were re-plaqued for viable persistent tumour

Participants
Number of participants allocated:
Total (*n*): 36
Treatment 1 (*n*): 16
Treatment 2 (*n*): 20

Number of eyes:
Total (*n*): 36
Treatment 1 (*n*): 16
Treatment 2 (*n*): 20

Number of tumours:
Total (*n*): not reported

continued

Dropouts:
Total (*n*): not reported

Age of participants:
Total (*n*): range 2 months to 4 years and 6 months

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 11 unilateral, 25 bilateral
Treatment 1 (*n*): 6 unilateral, 10 bilateral
Treatment 2 (*n*): 5 unilateral, 15 bilateral

Baseline tumour characteristics: Retinoblastoma classification (RE): (only reported for eyes that received brachytherapy)
Total (*n*): Not reported
Treatment 1 (*n*): group Ia = 1, group IIa = 9, group IIIa = 3, group IVa = 1, group Vb = 2
Treatment 2 (*n*): all patients had groups IV and V (number in each group not specified)

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Tumour regression

Treatment 1: 14/16 showed regression, 3/14 required second plaque owing to vitreous seeds, all showed >18 months with NED subsequently
Treatment 2: 16/20 described as "responded well"

Outcome 2
Description:
Requirement for enucleation postbrachytherapy

Treatment 1: 2/16
Treatment 2: 4/20

Outcome 3
Description:
Complications

Treatment 1: 2 cataracts, 1 vitreous haemorrhage
Treatment 2: 3 cataracts, 2 retinopathy, 2 papillopathy, 1 glaucoma, 2 vitreous haemorrhages. All patients had orbital bone hypoplasia

Outcome 4
Description:
Useful vision (ability to reach for small objects using only treated eye)

Treatment 1:14/16
Treatment 2: 10/20 (+5 with poor vision)

Outcome 5
Description:
Death

Treatment 1: 0/16
Treatment 2: 1/20

Publication details
Authors (year):
Antoneli *et al.* (2003)[130]

Country: Brazil

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To determine the clinical and epidemiological characteristics, and evaluate the outcome of two different treatment regimens with chemotherapy, surgery and radiation therapy in patients with extraocular retinoblastoma

Study design (brief details):
The treatment outcomes of 83 patients with newly diagnosed extraocular retinoblastoma who were treated at a single hospital with two different regimens were compared. In the first treatment period, from 1987 to 1991, patients were given cisplatin, teniposide, vincristine, doxorubicin, and cyclophosphamide, and in the second treatment period, from 1992 to 2000, patients were given cisplatin and teniposide with alternating courses of ifosfamide and etoposide

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
According to the treatment schedule for the hospital over the two different periods

Sample size calculations:
Not performed

Statistical analyses:
Kaplan–Meier curves were performed to compare 5-year overall survival, and 3- and 5-year disease-free survival for the different treatment regimens

Analysis by eyes or participants:
Participants

Inclusion criteria:
Not reported

Retinoblastoma classification system used:
CCG classification for extraocular retinoblastoma

Interventions
Treatment 1:
Treatment schedule for 1987–1991:
Patients with class I tumours were given cyclophosphamide and vincristine. Patients with class II–V were given induction therapy with cisplatin and teniposide
Patients without disease progression or recurrence after three cycles were subsequently given alternating regimens A and B. Regimen A consisted of cisplatin and teniposide. Regimen B consisted of doxorubicin, cyclophosphamide and vincristine. Intrathecal therapy consisted of methotrexate, cytarabine and dexamethasone

Dose, number of treatments, etc.:
Class I tumours:
Vincristine: one dose of 0.05 mg kg^{-1} per day or 1.5 mg m^{-2} per day; cyclophosphamide: one dose of 30 mg kg^{-1} per day or 900 mg m^{-2} per day every 21 days for ten cycles
Class II–V tumours:
Induction therapy: cisplatin: one dose of 90 mg m^{-2} per day, and teniposide: one dose of 100 mg m^{-2} per day every 21 days for three cycles
Maintenance therapy with regimen A: cisplatin: one dose of 90 mg m^{-2} per day, and teniposide: one dose of 100 mg per m^{-2} per day; and regimen B: cyclophosphamide: one dose of 30 mg m^{-2} per day; vincristine: one dose of 0.05 mg m^2 per day and doxorubicin: one dose of 2 mg per kg^{-1} per day for 60 weeks alternating between treatment regimen A and B every 21 days
Intrathecal therapy: methotrexate was given at a dose according to the age of the patient every 6 weeks (0.4 mg kg^{-1} per dose, maximum dose was 10 mg), cytarabine and dexamethasone

Period of treatment:
Class I tumours:
Chemotherapy was given for ten cycles of 21 days for class I tumours
Class II–V tumours:
Induction therapy was given for three cycles of 21 days followed by maintenance therapy of alternating regimen A and B every 21 days for a period of 60 weeks. Intrathecal methotrexate was given every 6 weeks during the treatment period

continued

Length of follow-up (mean, SD, range, etc.):
3- and 5-year survival curves were calculated

Adjunctive treatments:
EBRT dose was given concomitantly to the chemotherapy schedule using 40–50 Gy in 23 fractions of 2 Gy each (median total dose 46 Gy in 23 fractions of 2 Gy) in patients with class II–V. None of the patients with class I tumours received orbital EBRT
Patients with class I and II tumours were given enucleation at the time of diagnosis followed by the respective chemotherapy schedules. Patients with Class III–V received enucleation after three cycles of the induction chemotherapy regimen

Treatment 2:
Treatment schedule for 1992–2000:
Patients with class I–V were given induction therapy with ifosfamide and etoposide. Patients without disease progression or recurrence after three cycles were subsequently given alternating regimens A and B. Regimen A consisted of ifosfamide and etoposide. Regimen B consisted of cisplatin and tenoposide. Intrathecal therapy consisted of methotrexate and cytarabine and dexamethasone

Dose, number of treatments, etc.:
Class I–V tumours:
Induction therapy: ifosfamide: five doses at 1.8 mg m^{-2} per day and five doses of etoposide at 100 mg m^{-2} per day
Maintenance therapy with regimen A: ifosfamide: five doses at 1.8 mg m^{-2} per day and five doses of etoposide at 100 mg m^{-2} per day, and regimen B: cisplatin: one dose of 90 mg m^{-2} per day and one dose of teniposide at 100 mg m^{-2} per day for 34 weeks alternating between treatment regimen A and B every 21 days
Intrathecal therapy: methotrexate and cytarabine were given at a dose according to age. For patients aged <2 years the respective doses were 6 and 12 mg, >2–3 years 9 and 18mg, >3–9 years 12 and 24 mg, and >9 years 12 and 30 mg, and dexamethasone at a dose of 2 mg m^{-2} (maximum dose 2 mg)

Period of treatment:
Induction therapy was given every 21 days for three cycles followed by alternating regimen A and B every 21 days for a period of 34 weeks. Intrathecal methotrexate was given every 6 weeks during the treatment period

Length of follow-up (mean, SD, range, etc.):
3- and 5-year survival curves were calculated

Adjunctive treatments:
EBRT was given concomitantly to the chemotherapy schedule using 40–50 Gy in 23 fractions of 2 Gy each (median total dose 46 Gy in 23 fractions of 2 Gy) in patients with class II–V. None of the patients with class I tumours received orbital EBRT
Patients with class I and II tumours were given enucleation at the time of diagnosis followed by the respective chemotherapy schedules. Patients with class III–V received enucleation after three cycles of the induction chemotherapy regimen

Participants
Number of participants allocated:
Total (*n*): 83
Treatment 1 (*n*): 43
Treatment 2 (*n*): 40

Number of eyes:
Total (*n*): 103
Treatment 1 (*n*): 54
Treatment 2 (*n*): 49

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): 8 patients were lost to follow-up (the authors defined loss to follow-up as 2 missed consecutive medical consultations)

Age of participants:
Total: mean age at diagnosis was 32.9 months (range 2–145 months)
Treatment 1: 29.7 months
Treatment 2: 30.8 months

Baseline tumour characteristics: type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 63 unilateral, 20 bilateral
Treatment 1 (*n*): 32 unilateral, 11 bilateral
Treatment 2 (*n*): 31 unilateral, 9 bilateral

continued

Baseline tumour characteristics: Retinoblastoma classification (CCG):
Total (*n*): class I = 4 unilateral, 4 bilateral; class II = 21 unilateral, 8 bilateral; class III = 27 unilateral, 5 bilateral; class IV = 7 unilateral; class V = 4 unilateral, 3 bilateral
Treatment 1 (*n*): class I–III = 36; class IV and V = 7
Treatment 2 (*n*): class I–III = 33; class IV and V = 7

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
5-year overall survival according to treatment period (results according to classification of tumour)

Treatment 1: 55.1% (class I–III 65.3%, class IV and V 0%)
Treatment 2: 59.4% (class I–III 75.5%, class IV and V 20%)

$p = 0.690$ for comparison of overall survival between treatment periods
$p = 0.003$ for comparison of class I–III with class IV and V in treatment 1
$p < 0.001$ for comparison of class I–III with class IV and V in treatment 2

Outcome 2
Description:
5-year overall survival according to treatment periods in patients with unilateral tumours

Treatment 1: 44.6%
Treatment 2: 59.1%

No statistically significant difference between treatment periods

Outcome 3
Description:
3- and 5-year disease-free survival according to treatment period

Treatment 1: 59.6%
Treatment 2: 69.5%

There was no significant difference between treatment periods ($p = 0.351$). The authors state that disease-free survival estimates were equivalent for both 3 and 5 years.

Publication details
Authors (year):
Blach *et al.* (1996)[128]

Country: USA

Type of publication (full paper, abstract):
Full paper

Related publications:
McCormick *et al.* (1989)[154] and McCormick *et al.* (1988)[155]

Study design
Authors' objective:
To compare the long-term actuarial local control, eye conservation rate, survival and ocular complications in children with retinoblastoma treated with two different techniques of EBRT

Study design (brief details)
The treatment outcomes of 123 children with retinoblastoma referred from one setting for EBRT at a single centre were evaluated. The modified lateral beam (MLB) technique (used from 1984 to 1991) was compared with an anterior lens-sparing (ALS) technique (used from 1979 to 1984). Initial evaluation of children included ophthalmic examination under anaesthesia, routine blood work, cerebrospinal fluid cytology, bone marrow biopsy and a head CT scan or MRI to rule out extraocular extension and metastatic disease

continued

Retrospective/prospective:
Retrospective (obtained from McCormick *et al*., 1988)[155]

How patients were allocated to their treatment group:
The treatment received depended on when patients were referred for treatment. Treatment was changed from ALS to MLB technique in 1984 owing to an unacceptable number of local relapses requiring additional therapy in ALS-treated patients

Sample size calculations:
Not performed

Statistical analyses:
Kaplan–Meier survival curves were used to assess freedom from relapse, need for enucleation, cause-specific survival and overall survival. χ^2 tests were used to compare the two treatments for development of cataracts

Analysis by eyes or participants:
Eyes

Inclusion criteria:
Children referred to Memorial Sloan-Kettering Cancer Centre for EBRT from 1979 to 1991 from the New York Hospital–Cornell Medical Centre Ophthalmic Oncology Clinic

Retinoblastoma classification system used:
RE

Interventions

Treatment 1:
EBRT using an ALS technique

Dose, number of treatments, etc.:
A lateral D-shaped photon field was placed with the anterior border at the lateral bony rim of the orbit and irradiated 4 days per week. On day 5 an anterior electron beam field was used with a circular contact lens used in the eye as a lens shield. The dose ranged from 38.5 to 50 Gy in 2.5-Gy fractions

Period of treatment:
Not stated

Length of follow-up (mean, SD, range, etc.):
Mean 101 months (range 13–159 months)

Adjunctive treatments:
15% of the whole sample received chemotherapy for evidence of extraocular disease at the time of salvage enucleation, but none received initial systemic treatment

Treatment 2:
EBRT using an MLB technique

Dose, number of treatments, etc.:
A lateral D-shaped field was used with the anterior border placed at 2–3 mm posterior to the surgical limbus and the isocentre placed at the anterior border to avoid divergence into the lens. The dose ranged from 42 to 46 Gy in 2-Gy fractions

Period of treatment:
Not stated

Length of follow-up (mean, SD, range, etc.):
Mean 52 months (range 4–108 months)

Adjunctive treatments:
15% of the whole sample received chemotherapy for evidence of extraocular disease at the time of salvage enucleation, but none received initial systemic treatment
Two lateral parallel opposed D-shaped photon fields were used for patients being treated for bilateral disease; patients with bilateral disease who had had a unilateral enucleation were treated with a single lateral D-shaped photon field, exiting through the fellow socket; for patients with unilateral disease a single modified Schipper (1983) single oblique field was used. A tight-fitting head and neck plaster cast was taken and moulded onto a 'papoose board' for immobilisation

Note: Cryotherapy, photocoagulation, reirradiation or plaque therapy was used to treat eyes that relapsed after irradiation. Enucleation was used for failure of salvage therapy or if the relapse was too advanced to use focal methods

continued

Participants
Number of participants allocated:
Total (*n*): 123

Number of eyes:
Total (*n*): 180
Treatment 1 (*n*): 67
Treatment 2 (*n*): 113

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported (not applicable)

Age of participants:
Total: not reported

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): bilateral $n = 104$; unilateral $n = 19$

Baseline tumour characteristics: Retinoblastoma classification (RE)
Total (*n*): group I = 41, group II = 32, group III = 22, group IV = 13, group V = 72
Treatment 1 (*n*): group I = 16 (24%), group II = 10 (15%), group III = 9 (13%), group IV = 5 (7%), group V = 27 (40%)
Treatment 2 (*n*): group I = 25 (22%), group II = 22 (19%), group III = 13 (12%), group IV = 8 (7%), group V = 45 (40%)

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Note: The authors state that the two treatment groups were balanced in relation to RE classification, number of unilateral eyes, initial age at diagnosis, administration of chemotherapy and family history of retinoblastoma (data reported for RE classification only)

Results:

Outcome 1
Description:
Local control: freedom from relapse (%) at 5 years and 8 years (relapse or local failure was defined as the need for any additional treatment to the irradiated eye)

Treatment 1:
RE group I–III (35 eyes): 5 years 37%, 8 years 37%
RE group IV–V (32 eyes): 5 years 38%, 8 years 34%
RE group I–V (67 eyes): 5 years 38%, 8 years 38%
Treatment 2:
RE group I–III (61 eyes): 5 years 84%, 8 years 84%
RE group IV–V (52 eyes): 5 years 50%, 8 years 50%
RE group I–V (113 eyes): 5 years 65%, 8 years 65%

Group I–V eyes: treatment 1 vs treatment 2, $p = 0.0001$
Group I–III eyes: treatment 1 vs treatment 2, $p < 0.0001$
Group IV–V eyes: treatment 1 vs treatment 2, ns (at 8 years)

Outcome 2
Description:
Eye survival (no enucleation required) at 5 years and 8 years

Treatment 1:
RE group I–III (35 eyes): 5 years 85%, 8 years 81%
RE group IV–V (32 eyes): 5 years 60%, 8 years 60%
RE group I–V (67 eyes): 5 years 73%, 8 years 71%
Treatment 2:
RE group I–III (61 eyes): 5 years 94%, 8 years 94%
RE group IV–V (52 eyes): 5 years 61%, 8 years 61%
RE group I–V (113 eyes): 5 years 78%, 8 years 78%

continued

Group I–V eyes: treatment 1 vs treatment 2, ns
Group I–III eyes: treatment 1 vs treatment 2, ns
Group IV–V eyes: treatment 1 vs treatment 2, ns

Outcome 3
Description:
Development of cataracts

Across both groups 22% of eyes developed cataracts. The authors report that there was no difference in cataract development between the two treatment techniques

Outcome 4
Description:
Cause-specific and overall survival

Across both groups actuarial cause-specific survival was 94% at 5 and 8 years and actuarial overall survival was 87% at 5 and 8 years. The authors report that there was no difference between the two treatment groups on these outcomes

ALS, anterior lens-sparing; MLB, modified lateral beam; ns, not significant.

Publication details
Authors, (year):
Cassady *et al.* (1969)[109]

Country: USA

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To determine the local tumour control rate in patients treated with radiation, the effect of radiation dose on subsequent vision, the use of TEM in conjunction with radiation, and the effectiveness of more than one course of irradiation on recurrent disease

Study design (brief details):
The medical records of all children treated with radiation therapy for retinoblastoma at the Institute of Ophthalmology, Columbia Presbyterian Medical Centre, from 1954 to 1963 were reviewed with the above objective in mind

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not stated, although likely to be according to the treatment actually received as per hospital protocol

Sample size calculations:
Not reported

Statistical analyses:
No statistical comparisons between the treatment groups were performed

Analysis by eyes or participants:
Eyes

Inclusion criteria:
The stage of disease at time of initial treatment had to be reported

Retinoblastoma classification system used:
RE

Notes: The results are presented here only for outcomes where different treatment groups were compared. The number of recurrences and need for further treatment are not reported as the results are presented according to the stage of disease, not the treatment received

Interventions:
Treatment 1:
Intra-arterial TEM and radiation therapy

continued

Dose, number of treatments, etc.:
Radiation was given three times a week using 3.33–4 Gy to deliver a total dose of 32.5–45 Gy. TEM was given at a dose of 0.08 mg kg^{-1}

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Not reported

Adjunctive treatments:
Not reported

Treatment 2:
Intramuscular TEM and radiation therapy

Dose, number of treatments, etc.:
Radiation was given three times a week using 3.33–4 Gy to deliver a total dose of 32.5–45 Gy. TEM was given at a dose of 0.08 mg per kg^{-1}

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Up to 10 years

Adjunctive treatments:
Not reported

Treatment 3:
Irradiation alone

Dose, number of treatments, etc.:
Radiation was given three times a week using 33.3–4 Gy to deliver a total dose of 32.5–45 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Up to 10 years

Adjunctive treatments:
Not reported

Subgroup analysis according to the dose of radiation
Subgroup 1:
Radiation delivered at <40 Gy

Dose, number of treatments, etc.:
Radiation was given three times a week using 3.3–4 Gy to deliver a total dose of 1<40 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Not reported

Adjunctive treatments:
TEM was given at a dose of 0.08 mg per kg^{-1} to some patients

Subgroup 2:
Radiation delivered at >40 Gy

Dose, number of treatments, etc.:
Radiation was given three times a week using 3.3 to 4.0 Gy to deliver a total dose of >4000 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Not reported

Adjunctive treatments:
TEM was given at a dose of 0.08 mg per kg^{-1} to some patients

continued

Participants
Number of participants allocated:
Total (*n*): 230

Number of eyes:
Total (*n*): 223
Treatment 1 (*n*): 98
Treatment 2 (*n*): 44
Treatment 3 (*n*): 81

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported

Age of participants:
Total: 48 aged <6 months, 54 aged 6 months to 1 year, 63 aged 1–2 years, 37 aged 2–3 years, 13 aged 3–4 years, 7 aged 4–5 years, and 8 aged >5 years

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): not reported

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): group I = 43, group II = 45, group III = 32, group IV = 37, group V = 66
Treatment 1 (*n*): group I = 3, group II = 15, group III = 11, group IV = 20, group V = 49
Treatment 2 (*n*): group I = 16, group II = 13, group III = 8, group IV = 4, group V = 3
Treatment 3 (*n*): group I = 24, group II = 17, group III = 13, group IV = 13, group V = 14

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results:

Outcome 1
Description:
Local tumour control (definition not given)

Treatment 1: overall 35/98 patients had improved (group I 3/3, group II 10/15, group III 8/11, group IV 6/20, group V 8/49)
Treatment 2: overall 28/44 patients had improved (group I 13/16, group II 10/13, group III 5/8, group IV 0/4, group V 0/3)
Treatment 3: overall 46/81 patients had improved (group I 20/24, group II 10/17, group III 9/13, group IV 5/13, group V 2/14)

Outcome 2: Subgroup analysis according to the dose of radiation
Description:
Local tumour control (definition not given) according to dose of radiation

Subgroup 1 (≤ 40 Gy): overall 30/73 patients had improved (group I 9/9, group II 5/11, group III 8/10, group IV 4, group V 4/15)
Subgroup 2 (>40 Gy): overall 79/150 patients had improved (group I 27/34, group II 25/34, group III 14/22, group IV 7/22, group V 6/38)

Outcome 3: Subgroup analysis according to the dose of radiation
Description:
Quality of vision (number of patients) following treatment with radiation at a dose of ≤ 40 Gy and >40 Gy

Subgroup 1 (<40 Gy): good 69, fair 6, poor or absent 4
Subgroup 2 (>40 Gy): good 21, fair 3, poor or absent 0

Outcome 4: Subgroup analysis according to the TEM
Description:
Local tumour control rate (definition not given) according to those treated intra-arterially with TEM or 'other' (intramuscularly or with radiation alone)

Treatment 1 (intra-arterially with TEM): overall 35/98 patients had improved (group I 3/3, group II 10/15, group III 8/11, group IV 6/20, group V 8/49)
Treatment 2 ('other'): overall 74/125 patients had improved (group I 33/44, group II 20/30, group III 14/21, group IV 5/15, group V 2/17)

Publication details
Authors (year):
Draper *et al.* (1986)[126]

Country: UK

Type of publication (full paper, abstract):
Full paper

Note: Hawkins *et al.* (1986)[156] performed a similar study to examine the risk of SPTs, in relation to therapy among survivors of all childhood cancers, including retinoblastoma. However, the authors report that patients with retinoblastoma were followed up more intensively and studied separately in the study presented herein

Study design
Authors' objective:
To determine the incidence rate of SPTs among patients treated for retinoblastoma in Britain from 1950 to 1977 associated with treatment modality and whether the patient had genetic or non-genetic retinoblastoma

Study design (brief details):
The records of children with retinoblastoma were reviewed form the National Cancer Registration Scheme (1962–1977) and from cancer registries and hospital records for earlier years. Follow-up information was also obtained from GPs, hospital records and national record systems. Information was obtained on the survivors who were found to have developed a secondary tumour to determine whether treatment modality and classification of retinoblastoma were associated with subsequent tumour development

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not stated

Sample size calculations:
Not performed

Statistical analyses:
The number of people with SPTs was obtained, and cumulative incidence rates for SPTs were derived from all patients in the series, using methods to adjust for different lengths of follow-up

Analysis by eyes or participants:
Participants

Inclusion criteria:
For the years 1962–1977, all cases notified to the National Cancer Registration Scheme were eligible for inclusion. For earlier years, only 3-year survivors from retinoblastoma identified at certain hospitals and cancer registries were included

Retinoblastoma classification system used:
Not reported

Note: The authors also identified a further nine patients with retinoblastoma who went on to develop secondary neoplasms. These patients were not included as part of the follow-up series and will therefore not be included in this review as they have been selected on the basis of their outcome and might introduce bias into the results

Interventions
Treatment 1:
Radiotherapy including EBRT or brachytherapy (using cobalt or radium plaques)

Dose, number of treatments, etc.:
Where reported, EBRT was administered at doses ranging from 15 to 80 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
The interval since retinoblastoma to developing an SPT ranged from 31 to 220 months

Adjunctive treatments:
Enucleation was performed in some patients

Treatment 2:
Chemotherapy consisting of cyclophosphamide, with or without other drug combinations

Dose, number of treatments, etc.:
Not reported

continued

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
The interval since retinoblastoma to developing an SPT ranged from 31 to 220 months

Adjunctive treatments:
Enucleation was performed in some patients

Treatment 3:
Chemotherapy and radiotherapy. Chemotherapy consisted of cyclophosphamide, with or without other drug combinations, and radiotherapy included EBRT or brachytherapy (using cobalt or radium plaques)

Dose, number of treatments, etc.:
Where reported, EBRT was administered at doses ranging from 15 to 80 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
The interval since retinoblastoma to developing an SPT ranged from 31 to 220 months

Adjunctive treatments:
Enucleation was performed in some patients

Treatment 4:
Enucleation (no chemotherapy or radiotherapy was given)

Dose, number of treatments, etc.:
Not applicable

Period of treatment:
Not applicable

Length of follow-up (mean, SD, range, etc.):
The interval since retinoblastoma to developing an SPT ranged from 31 to 220 months

Adjunctive treatments:
None

Participants
Number of participants allocated:
Total (*n*): 882

Treatment 1 (*n*): 319
Treatment 2 (*n*): 11
Treatment 3 (*n*): 95
Treatment 4 (*n*): 457

Number of eyes:
Total (*n*): not reported

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported

Age of participants:
Total: age at diagnosis ranged from 1 to 28 months

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 384 genetic and 498 non-genetic cases
Treatment 1 (*n*): 241 genetic, 78 non-genetic
Treatment 2 (*n*): 3 genetic, 8 non-genetic
Treatment 3 (*n*): 73 genetic, 22 non-genetic
Treatment 4 (*n*): 67 genetic, 390 non genetic

Baseline tumour characteristics: Retinoblastoma classification (RE or equivalent):
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

continued

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Number of participants who went on to develop an STP (type of neoplasm)

Treatment 1: 16 (1 osteosarcoma nasal bones, 2 osteosarcoma femur, 1 osteosarcoma tibia, 4 osteosarcoma orbit, 1 anaplastic fibrosacroma, 1 acute lymphatic leukaemia, 1 astrocytoma suprasellar, 1 meningioma (benign), 1 malignant melanoma to the forehead, 1 breast carcinoma, 1 liposarcoma, 1 stomach sarcoma)
Treatment 2: 1 (osteosarcoma tibia)
Treatment 3: 9 (1 osteosarcoma tibia, 1 osteosarcoma maxilla, 3 osteosarcoma femur, 2 osteosarcoma orbit, 1 fibrosacroma orbit, 1 glioblastoma temporal lobe)
Treatment 4: 4 (1 osteosarcoma tibia, 1 osteosarcoma fibula, 1 adenocarcinoma cervix, leiomyosarcoma to temple and sebaceous carcinoma eyelid, and 1 carcinoma oesophagus)

Outcome 2
Description:
Cumulative incidence rates (calculated) of all SPTs (osteosarcomas) among all patients with genetic retinoblastoma at 12 years and 18 years

All sites: 4.3% at 12 years, 8.4% at 18 years (3.6% at 12 years, 6% at 18 years)
Inside the field of radiation for patients who received radiotherapy: 3.4% at 12 years, 6.6% at 18 years (2.4% at 12 years, 3.7% at 18 years)
Outside the field of radiation (all patients): 1.6% at 12 years, 3.0% at 18 years (1.6% at 12 years, 3% at 18 years)
Outside the field of radiation (patients who did not receive chemotherapy): 1.0% at 12 years, 2.2% at 18 years (1.0% at 12 years, 2.2% at 18 years)

Outcome 3
Description:
Cumulative incidence rates (calculated) of SPTs among patients with genetic retinoblastoma treated between 1962 and 1977: patients treated with chemotherapy (treatment 2) were compared with those who did not receive chemotherapy (treatment 1, 3 and 4)

Treatment 1: 4.2% at 12 years, 4.2% at 18 years
Treatment 3: 6.5% at 12 years, 14.7% at 18 years
Treatment 4: 0% at 12 years, 0% at 18 years

Outcome 4
Description:
Cumulative incidence rates (calculated) of SPTs among patients with genetic retinoblastoma inside and outside the fields of radiation

Treatment 1: inside the field of radiation: 2.9% at 12 years , 2.9% at 18 years
Treatment 3: inside the field of radiation: 4.2% at 12 years, 9.9% at 18 years
Chemotherapy with or without radiotherapy: outside the field of radiation: 4.6% at 12 years ,7.5% at 18 years
Other treatment (including radiotherapy, but without chemotherapy): outside the field of radiation: 1.0% at 12 years, 1.0% at 18 years

Publication details
Authors (year):
Foote *et al*. (1989)[113]

Country: USA

Type of publication (full paper, abstract):
Full paper

Related publication:
Schomberg *et al*.[136] provide more recent data in an abstract. Where relevant these data have been inserted below, but the Foote *et al*.[113] publication has been extracted as the main publication as it provides more information on study design

Study design
Authors' objective:
To determine the effect of EBRT and radiation dose on tumour control in patients with retinoblastoma

Study design (brief details):
The medical records of patients with retinoblastoma treated at the Mayo Clinic between 1977 and 1987 with EBRT were reviewed to determine the effect of treatment technique and radiation dose on tumour control. Patients were also examined by binocular indirect ophthalmoscopy with scleral indentation halfway through radiation therapy, at the end of therapy, and at 1–6-month interval follow-up. (Schomberg *et al*. examined the medical records of patients from 1977 to 1989[136])

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Determined by the treating physician, the size and location of the tumours and the presence/absence of seeding. Smaller tumours located posterior to the equator were treated by the lateral field technique. Larger tumours located at or extending anterior to the equator, or those that involved the ora serrata, or with vitreous seeding were treated using the anterior field technique
Early in the study the lateral field was the most common technique, and the anterior technique was the most common technique later when recurrences were noted

Sample size calculations:
Not performed

Statistical analyses:
Not stated. The number of eyes with the outcome of interest was reported. No statistical comparisons were performed between treatment groups. The authors also performed a dose–response analysis for the combined treatment groups (not extracted for this review)

Analysis by eyes or participants:
Eyes and participants

Inclusion criteria:
Not reported

Retinoblastoma classification system used:
RE

Interventions
Treatment 1:
Lateral technique: EBRT using a single, shaped, lateral field temporal field by using a beam-splitting block positioned in the anterior aspect of the field at the central axis, with (6 eyes) or without (8 eyes) posterior angulation of the beam

Dose, number of treatments, etc.:
Total EBRT dose administered was 39–51 Gy in 1.8–3.0 Gy fractions (for both treatments combined)

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
For the updated study the median length of follow-up was 71.6 months for both treatment groups combined[136]

Adjunctive treatments:
One child received chemotherapy; one child received photocoagulation or cryotherapy before radiation therapy

Treatment 2:
Anterior technique: EBRT using an anterior shaped field with paired, wedged anterior oblique fields, an anterior field alone, or an anterior field combined with an oblique or lateral field. No lens block was used

continued

Dose, number of treatments, etc.:
Total EBRT dose administered was 39–51 Gy in 1.8–3.0 Gy fractions (for both treatments combined)

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
For the updated study the median length of follow-up was 71.6 months for both treatment groups combined[136]

Adjunctive treatments:
One child received chemotherapy, one child received photocoagulation or cryotherapy before radiation therapy

Participants

Number of participants allocated:
Total (*n*): 22 (from Schomberg *et al.*[136])

Number of eyes:
Total (*n*): 30 (from Schomberg *et al.*[136])
Treatment 1 (*n*): 14
Treatment 2 (*n*): 16

Number of tumours:
Total (*n*): median number of tumours per eye was 3 (range 1–27)

Dropouts:
Total (*n*): not reported

Age of participants:
Total: median age was 4.6 months (range 0.5–39.2 months), although this did not include the additional four patients from the updated study

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 3 unilateral and 15 bilateral; 5 had a known family history, 13 did not. However, information is not available on the four additional patients in the updated study

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): group I–III = 18, group IV–V = 12 (from Schomberg *et al.*[136])
Treatment 1 (*n*): group I–III = 10, group IV–V = 4
Treatment 2 (*n*): group I–III = 8, group IV–V = 8

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results

Outcome 1

Description:
Number of eyes given additional treatment (from Schomberg *et al.*[136])

Treatment 1: 10/14 (71%)
Treatment 2: 8/16 (50%)[a]

[a] The abstract states this figure as 22%, but presumably this is an error

Three patients overall developed second malignancies

Outcome 2

Description:
Proportion of eyes developing cataracts (from Schomberg *et al.*[136])

Treatment 1: 29%
Treatment 2: 63%

Cataracts developed in 14 eyes overall at a median of 29 months

Outcome 3

Description:
Mortality (from Schomberg *et al.*[136])

There were no patient deaths in either treatment group

Publication details
Authors (year):
Guenduez *et al*. (1998)[134]

Country: USA

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To determine the outcome of chemoreduction treatment in patients with RE group V

Study design (brief details):
Data were prospectively gathered from 22 consecutive patients with RE group V retinoblastoma treated at the Wills Eye Hospital between 1994 and 1996. The outcomes of patients who received two-cycle or six-cycle chemoreduction were compared in terms of avoiding EBRT and enucleation

Retrospective/prospective:
Prospective

How patients were allocated to their treatment group:
The treatment allocated was according to hospital protocol. The protocol was initially for two cycles of chemotherapy and was later changed to a six-cycle protocol to achieve better long-term tumour control.[133] Choice of focal treatment was made on an individual tumour basis

Sample size calculations:
Not stated

Statistical analyses:
ANOVA and Wilcoxon tests were used to compare the baseline characteristics of the two groups. Logistic regression analysis was used to compare the treatment groups

Analysis by eyes or participants:
Eyes

Inclusion criteria:
Patients with RE group V retinoblastoma, in one or both eyes, treated with chemoreduction between August 1994 and July 1996 at Wills Eye Hospital were eligible for inclusion. Exclusion criteria were: iris neovascularisation or tumour invasion into the pars plana, anterior chamber, choroids, orbit or optic nerve; liver, kidney or ear problems. Informed consent was obtained

Retinoblastoma classification system used:
RE

Interventions
Treatment 1:
Two-cycle chemoreduction

Dose, number of treatments, etc.:
Vincristine sulphate, 1.5 mg m^{-2} (0.05 mg kg^{-1} for children 36 months or younger; maximum dose 2 mg); etoposide, 150 mg m^{-2} (5 mg kg^{-1} for children 36 months or younger); and carboplatin, 560 mg m^{-2} (18.6 mg kg^{-1} for children 36 months or younger)
Day 0, vincristine, etoposide, carboplatin were given; day 1, etoposide; day 7, vincristine; day 14, vincristine. The regimen was repeated every 3–4 weeks twice

Period of treatment:
2 months

Length of follow-up (mean, SD, range, etc.):
Mean 24 months (median 25 months, range 20–32 months) (for both treatment groups combined)

Adjunctive treatments:
Focal treatment including laser photocoagulation, transpupillary thermotherapy, cryotherapy and plaque radiotherapy

Treatment 2:
Six-cycle chemoreduction

Dose, number of treatments, etc.:
Vincristine sulphate, 1.5 mg m^{-2} (0.05 mg kg^{-1} for children 36 months or younger; maximum dose 2 mg); etoposide, 150 mg m^{-2} (5 mg kg^{-1} for children 36 months or younger); and carboplatin, 560 mg m^{-2} (18.6 mg kg^{-1} for children 36 months or younger)
Day 0, vincristine, etoposide, carboplatin were given; Day 1, etoposide. The regimen was repeated every 3–4 weeks six times

continued

Period of treatment:
6 months

Length of follow-up (mean, SD, range, etc.):
Mean 24 months (median 25 months, range 20–32 months) (for both treatment groups combined)

Adjunctive treatments:
Focal treatment including laser photocoagulation, transpupillary thermotherapy, cryotherapy and plaque radiotherapy

Participants

Number of participants allocated:
Total (*n*): 22
Treatment 1 (*n*): 13
Treatment 2 (*n*): 9

Number of eyes:
Total (*n*): 27
Treatment 1 (*n*): 16
Treatment 2 (*n*): 11

Number of tumours: median total number of tumours per eye:
Total (*n*): not stated
Treatment 1 (*n*): 3
Treatment 2 (*n*): 3

Dropouts:
Total (*n*): not stated
Treatment 1 (*n*): not stated
Treatment 2 (*n*): not stated

Age of participants: median age at diagnosis:
Total: not stated
Treatment 1: mean 16 months (median 11 months, range 2– 46 months)
Treatment 2: mean18 months (median 12 months, range 3–42 months)

Baseline tumour characteristics: Type of retinoblastoma:
Total (*n*): not stated

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): group Va 19, group Vb 8
Treatment 1 (*n*): group Va = 11, group Vb = 5
Treatment 2 (*n*): group Va = 8 eyes, group Vb = 3

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): 12 eyes
Treatment 1 (*n*): 7
Treatment 2 (*n*): 5

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): 14 eyes
Treatment 1 (*n*): 8
Treatment 2 (*n*): 6

Other relevant baseline/tumour characteristics (subretinal fluid, median largest tumour diameter, median tumour thickness):
Total (*n*): subretinal fluid, 15 eyes
Treatment 1 (*n*): subretinal fluid, 10 eyes; tumour diameter, median = 17 mm; tumour thickness median = 7 mm
Treatment 2 (*n*): subretinal fluid, 5 eyes; tumour diameter, median = 16 mm; tumour thickness median = 7 mm

There were no statistically significant differences between the two treatment groups with respect to any of the above baseline characteristics

Result

Outcome 1

Description:
Number (%) of patients requiring EBRT following chemoreduction and focal therapy

Treatment 1: 12/16 eyes (75%)
Treatment 2: 4/11 eyes (36%)

There was no statistical difference between the two treatment groups ($p = 0.28$)

continued

Outcome 2
Description:
Number of patients eventually requiring enucleation global salvage rate

Treatment 1: 4/4 of the eyes (0% global salvage) for patients treated with chemoreduction and focal treatment; 3/12 (75% global salvage) of the eyes that were treated with EBRT following chemoreduction and focal therapy
(In the non-irradiated group three eyes were enucleated owing to persistent tumour and seeds and one vitreous haemorrhage; in the irradiated group three eyes were enucleated owing to recurrent tumour and seeds)
Treatment 2: 2/7 (71% global salvage) of the eyes that were treated with chemoreduction and focal treatment; 1/4 (75% global salvage) of the eyes that were treated with EBRT following chemoreduction and focal therapy
(In the non-irradiated group one eye was enucleated owing to non-responsive advanced intraocular disease and one owing to vitreous haemorrhage. In the irradiated group one eye was enucleated owing to vitreous seed recurrence)
The global salvage rate was significantly lower in the two-cycle chemoreduction group that did not receive external beam radiotherapy ($p = 0.03$). There were no significant differences between the other groups

ANOVA, analysis of variance.

Publication details
Authors (year):
Hadjistilianou *et al*. (1991)[108]

Country: Italy

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To analyse the occurrence of new retinoblastoma and recurrences during and after focal treatment or external radiotherapy of the less involved eye in bilateral cases

Study design (brief details):
Records of children with bilateral retinoblastoma who were treated at the Siena University Eye Institute between 1960 and 1990 were identified. Occurrence of new tumour, time to new tumour, recurrence and time to recurrence were determined for those treated exclusively with light coagulation and those treated initially with EBRT

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not explicitly stated, but probably by severity of presenting disease (more of those who received radiotherapy had advanced disease)

Sample size calculations:
Not reported

Statistical analyses:
No statistical comparisons of results between treatment groups were performed

Analysis by eyes or participants:
Participants

Inclusion criteria:
Children with bilateral retinoblastoma treated at the Siena University Eye Institute between 1960 and 1990 were studied

Retinoblastoma classification system used:
RE

Interventions

Treatment 1:
Light or photocoagulation, after enucleation of the worse eye

Dose, number of treatments, etc.:
Not reported

continued

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Not reported

Adjunctive treatments:
Not reported

Treatment 2:
EBRT, after enucleation of the worse eye

Dose, number of treatments, etc.:
Not reported

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Not reported

Adjunctive treatments:
Not reported

Participants
Number of participants allocated:
Total (*n*): 23
Treatment 1 (*n*): 7
Treatment 2 (*n*): 16

Number of eyes:
Total (*n*): 23
Treatment 1 (*n*): 7
Treatment 2 (*n*): 16

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): 32 patients were originally identified; 3 were lost to follow-up and 6 were subsequently excluded (5 underwent bilateral enucleation and 1 spontaneously regressed)

Age of participants:
Total: not reported
Treatment 1: 6.7 months
Treatment 2: 12.2 months

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): all 23 were bilateral

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): group I = 6, group II = 7, group III = 7, group IV = 2, group V = 1
Treatment 1 (*n*): group I = 4, group II = 3
Treatment 2 (*n*): group I = 2, group II = 4, group III = 7, group IV = 2, group V = 1

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Occurrence of new tumours (defined as tumours not present at time of focal treatment or EBRT, but subsequently appeared and were treated with cryo- and photocoagulation)

Treatment 1: total 12 new tumours in 6 eyes; RE I 6 new in 3 eyes; RE II 6 new in 3 eyes
Treatment 2: total 5 new tumours in 3 eyes; RE I 1 new in 1 eye; RE II 2 new in 1 eye; RE III 2 new in 1 eye

continued

Outcome 2
Description:
Months to occurrence of new tumours

Treatment 1: mean 7.6 months (range 2–19 months) (stage I 2–12 months; stage II 2–19 months)
Treatment 2: mean 9.5 months (range 2–15 months) (stage I 15 months; stage II 9 months; stage III 2–12 months)

Outcome 3
Description:
Recurrent tumours (defined as a tumour growth which originates, after successful treatment, at the margin or within the scar of the inactive, regressed tumour)

Treatment 1: total 4 in 3 eyes; RE I 3 in 2 eyes; RE II 1 in 1 eye
Treatment 2: total 5 in 4 eyes; RE I 1 in 1 eye; RE II 2 in 2 eyes; RE III 2 in 1 eye

Outcome 4
Description:
Months to recurrence of tumours

Treatment 1: mean 11 months (range 8–13 months) (stage I 8–13 months; stage II 12 months)
Treatment 2: mean 10.6 months (range 3–18 months) (stage I 3 months; stage II 11 months; stage III 12–18 months)

Publication details
Authors (year):
Hauffa *et al*. (1995)[125]

Country: Germany

Type of publication (full paper, abstract):
Full paper (German language)

Study design
Authors' objective:
To evaluate growth and development in children who had received surgery, irradiation or chemotherapy for the treatment of retinoblastoma

Study design (brief details):
Patients who had undergone surgery, radiotherapy with or without chemotherapy for the treatment of bilateral retinoblastoma were re-examined with the above objective in mind

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not reported

Sample size calculations:
Not reported

Statistical analyses:
The mean difference and SD for each treatment group were reported

Analysis by eyes or participants:
Participants

Inclusion criteria:
Patients with bilateral retinoblastoma were eligible for inclusion

Retinoblastoma classification system used:
Not reported

Note: The study used biological tests to investigate the impact of treatment modality on pubertal development and serum concentrations of growth hormones. However, as this review is only concerned with clinical outcomes, data on growth and endocrine levels will not be reported

Interventions
Treatment 1: Radiation using 200–300-kV X-ray

Dose, number of treatments, etc.:
X-rays were used to deliver 10 Gy per week in fractions of 0.2 Gy. Total median dose given was 44 Gy (range 36–84 Gy)

continued

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median follow-up post-treatment was 14.8 years (range 5.3–24.2 years)

Adjunctive treatments:
21/37 patients also received chemotherapy
4/37 patients also received orbital radiation

Treatment 2:
Radiation using ^{60}Co or ^{137}Cs isotopes

Dose, number of treatments, etc.:
Radiation was delivered at a dose of 10 Gy per week in fractions of 2, 2.5 or 3.3 Gy. Total median dose was 59 Gy (range 40–127 Gy)

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median follow-up post-treatment was 14.8 years (range 5.3–24.2 years)

Adjunctive treatments:
5/12 patients also received chemotherapy
7/12 patients also received orbital radiation

Treatment 3:
Radiation delivered using 5.7-MeV linear lateral accelerator or two opposed lateral temporal fields

Dose, number of treatments, etc.:
Radiation dose of 10 Gy per week in fractions of 3.3 Gy. Total median dose was 42 Gy (range 40–48 Gy)

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median follow-up post-treatment was 14.8 years (range 5.3–24.2 years)

Adjunctive treatments:
2/31 patients also received orbital radiation
4/31 patients also received chemotherapy

Treatment 4:
Surgery only

Dose, number of treatments, etc.:
Not applicable

Period of treatment:
Not applicable

Length of follow-up (mean, SD, range, etc.):
Median follow-up post-treatment was 14.8 years (range 5.3–24.2 years)

Adjunctive treatments:
One patient underwent bilateral enucleation and 10 patients underwent unilateral enucleation. Of the patients who underwent unilateral enucleation, 5 were also given photocoagulation, and 5 were given photocoagulation and cryotherapy of the contralateral eye

Participants
Number of participants allocated:
Total (*n*): 92
Treatment 1 (*n*): 37
Treatment 2 (*n*): 12
Treatment 3 (*n*): 31
Treatment 4 (*n*): 12

Number of eyes:
Total (*n*): not reported

Number of tumours:
Total (*n*): not reported

continued

Dropouts:
Total (*n*): not applicable

Age of participants:
Total: median 15.8 years (range 6–24.9 years)
Treatment 1: 21.1 years (range 15.6–24.8 years)
Treatment 2: 10.4 years (range 6.6–17.7 years)
Treatment 3: 11.9 years (range 6 to 16.4 years)
Treatment 4: 16.5 years (range 16.7–24.9 years)

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 92 patients with bilateral retinoblastoma
Treatment 1 (*n*): 37 bilateral
Treatment 2 (*n*): 12 bilateral
Treatment 3 (*n*): 31 bilateral
Treatment 4 (*n*): 12 bilateral

Baseline tumour characteristics: Retino classification (Reese-Ellsworth or equivalent):
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results

Outcome 1
Description:
Height of participants normalised by expressing SDS according to the mean for age and gender of participants reported as mean height score and SD

Treatment 1: 0.22 (1.1)
Treatment 2: 0.25 (0.9)
Treatment 3: 0.35 (1.3)
Treatment 4: 0.71 (1.5)

The authors report that there was no difference between treatment groups (*p*-value not given)

Publication details
Authors (year):
Haye *et al.* (1989)[127]

Country: France

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To undertake a retrospective study of 105 cases of retinoblastoma treated in an institution from 1977 to 1981

Study design (brief details):
The authors reviewed the cases of 105 children treated in one institution from 1977 to 1981

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Patients were allocated based on disease presentation. RE stage I–IV tumours were treated with primary EBRT or brachytherapy. Stage V tumours received primary chemotherapy and EBRT

Sample size calculations:
Not stated

Statistical analyses:
Specific analyses used not stated. Significance level stated to be $p > 0.05$

continued

Analysis by eyes or participants:
Participants

Inclusion criteria:
Not stated

Retinoblastoma classification system used:
RE

Interventions

Treatment 1:
Primary radiotherapy: either EBRT or brachytherapy using ^{60}Co radioactive plaques

Dose, number of treatments, etc.:
Not stated

Period of treatment:
Not stated

Length of follow-up (mean, SD, range, etc.):
Minimum of 5 years

Adjunctive treatments:
Not stated

Treatment 2:
Primary chemotherapy using vincristine, actinomycin and cyclophosphamide

Dose, number of treatments, etc.:
Two courses, followed by a further six courses after EBRT. Dose not stated

Period of treatment:
Not stated

Length of follow-up (mean, SD, range, etc.):
Minimum of 5 years

Adjunctive treatments:
EBRT
Additional treatment given 'if necessary' included brachytherapy using ^{60}Co radioactive plaques, xenon arc photocoagulation, radiotherapy to the orbital socket and brain and intensive chemotherapy with CCNU (lomustine) and adriamycin in cases of orbital recurrence or invasion of the cut end of the optic nerve; and prophylactic chemotherapy in cases with choroidal involvement. However, it is unclear whether this referred to both treatment groups

Participants
Number of participants allocated:
Total (*n*): 45 (these participants are part of an overall cohort of 105 patients; data comparing the treatments are available for RE group I and II patients only)
Treatment 1 (*n*): 33
Treatment 2 (*n*): 12

Number of eyes:
Total (*n*): not reported (for treatment comparison)

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported. However, overall 11 participants appear to be missing from the tables

Age of participants:
Total: mean age when first seen: 25 months (for the total cohort)

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): bilateral 65, unilateral 40 (for the total cohort)

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): group I = 19, group II = 26
Treatment 1 (*n*): group I = 17, group II = 16
Treatment 2 (*n*): group I = 2, group II = 10

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

continued

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Treatment success and failure

Treatment 1: group I: success $n = 16$, failure $n = 1$, group II: success $n = 13$, failure $n = 3$
Treatment 2: group I: success $n = 1$, failure $n = 1$, group II: success $n = 6$, failure $n = 4$

Publication details
Authors (year):
Honavar *et al*. (2002)[38]

Country: USA

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To evaluate the efficacy of adjuvant therapy given after enucleation in preventing metastasis in cases of high-risk retinoblastoma

Study design (brief details):
Retrospective non-randomised comparative study, with a concurrent comparison group. The medical records of all patients with unilateral sporadic retinoblastoma seen between 1974 and 1999 at a single centre, who had undergone enucleation and had predefined high-risk characteristics on histopathology reports, were identified for inclusion. The group that received adjuvant therapy and the group that did not were compared for incidence of metastasis

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Adjuvant therapy was administered as per hospital protocol or parental choice

Sample size calculations:
Not reported

Statistical analyses:
Baseline comparability between groups (adjuvant and non-adjuvant, also different chemotherapy regimens)/confounding factors were tested for using *t*-test for continuous variables and Fisher's exact test for discrete variables. Proportion of patients free of metastasis was calculated using Kaplan–Meier survival curves and groups were compared using the Cox proportional hazards regression model

Analysis by eyes or participants:
Participants

Inclusion criteria:
Patients with unilateral sporadic retinoblastoma who had undergone primary enucleation had no evidence of metastasis at diagnosis, and presented one or more of the following high-risk histopathological characteristics: anterior chamber seeding, iris, ciliary body, scleral or massive choroidal infiltration; invasion of optic nerve lamina cribrosa or retrolaminar optic nerve or optic nerve transaction; extrascleral extension

Retinoblastoma classification system used:
RE

Interventions
Treatment 1:
Enucleation plus adjuvant chemotherapy (vincristine sulphate + doxorubicin hydrochloride + cyclophosphamide before 1994, or vincristine + etoposide + carboplatin after 1994)

continued

Dose, number of treatments, etc.:
Pre-1994: vincristine sulphate 1.5 mg m^{-2} for 12 doses, six times per week, then at 21-day intervals. Doxorubicin hydrochloride at 60 mg m^{-2} for four doses at 21-day intervals. Cyclophosphamide at 300 mg m^2 for four doses and 600 mg m^{-2} for eight doses at 21-day intervals
Post-1994: vincristine sulphate 1.5 mg m^{-2} on day 1 of each cycle, carboplatin 560 mg m^{-2} on day 1 of each cycle, etoposide 150 mg m^2 on days 1 and 2 of each cycle. Six cycles given at 28-day intervals

Period of treatment:
6–12 months (mean 6.9 months, SD 1.4)

Length of follow-up (mean, SD, range, etc.):
Median 59 months (range 12–287 months)

Adjunctive treatments:
Intrathecal methotrexate (6–12 mg) in 12 patients with retrolaminar optic nerve invasion or invasion of optic nerve transaction; EBRT (40–45 Gy) in 14 patients with invasion of optic nerve transection, scleral infiltration or extrascleral extension

Treatment 2:
Enucleation with no adjuvant therapy

Dose, number of treatments, etc.:
Not applicable

Period of treatment:
All patients underwent enucleation 1 day to 2 weeks after diagnosis

Length of follow-up (mean, SD, range, etc.):
Median 59 months (range 12–287 months)

Adjunctive treatments:
None

Participants
Number of participants allocated:
Total (*n*): 80
Treatment 1 (*n*): 46
Treatment 2 (*n*): 34

Number of eyes:
Total (*n*): 80
Treatment 1 (*n*): 46
Treatment 2 (*n*): 34

Number of tumours:
Total (n): not reported

Dropouts:
Total (*n*): not applicable

Age of participants:
Total: median 33 months
Treatment 1: median 34 months (range 1 day to 16 years)
Treatment 2: median 30 months

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): all 80 were unilateral sporadic cases

Baseline tumour characteristics: Retinoblastoma classification (RE grade V):
Total (*n*): 79/80 (group Va = 18, group Vb = 61, group IVb = 1)
Treatment 1 (*n*): 45/46 (group V = 45, group IVb = 1)
Treatment 2 (*n*): 34/34 group V

Baseline tumour characteristics: Anterior chamber seeding:
Total (*n*): 24/80
Treatment 1 and 2 combined (*n*): 15/46
Treatment 3 (*n*): 9/34

Baseline tumour characteristics: iris infiltration:
Total (*n*): 4/80
Treatment 1 and 2 combined (*n*): 3/46
Treatment 3 (*n*): 1/34

continued

Baseline tumour characteristics: Ciliary body infiltration:
Total (*n*): 10/80
Treatment 1 and 2 combined (*n*): 7/46
Treatment 3 (*n*): 3/34

Baseline tumour characteristics: Massive choroidal infiltration:
Total (*n*): 29/80
Treatment 1 and 2 combined (*n*): 19/46
Treatment 3 (*n*): 10/34

Baseline tumour characteristics: Invasion of optic nerve lamina cribrosa:
Total (*n*): 13/80
Treatment 1 and 2 combined (*n*): 3/46
Treatment 3 (*n*): 10/34

Baseline tumour characteristics: Retrolaminar optic nerve invasion:
Total (*n*): 29/80
Treatment 1 and 2 combined (*n*): 19/46
Treatment 3 (*n*): 10/34

Baseline tumour characteristics: Invasion of optic nerve transection:
Total (*n*): 5/80
Treatment 1 and 2 combined (*n*): 5/46
Treatment 3 (*n*): 0/34

Baseline tumour characteristics: Scleral infiltration:
Total (*n*): 3/80
Treatment 1 and 2 combined (*n*): 2/46
Treatment 3 (*n*): 1/34

Baseline tumour characteristics: Extrascleral extension:
Total (*n*): 5/80
Treatment 1 and 2 combined (*n*): 5/46
Treatment 3 (*n*): 0/34

Results

Outcome 1
Description:
Presence of metastasis (all risk factors), median 9 months (range 6–57 months)

Treatment 1 and 2 combined: 2/46
Treatment 3: 8/34
$p = 0.02$ (Fisher's exact test)

Kaplan–Meier estimates showed that 96% of patients who received adjuvant therapy would remain free of metastasis at 10 years following enucleation compared with 76% of those who did not receive adjuvant therapy (Cox proportional hazards $p = 0.03$; hazard ratio 0.175, 95% CI 0.037 to 0.824)

The beneficial effect of adjuvant therapy was statistically significant in subgroups of patients with massive choroidal infiltration ($p = 0.04$) or retrolaminar optic nerve invasion ($p = 0.04$)

Outcome 2
Description:
Presence of metastasis in patients with single risk factors

Treatment 1 and 2 combined: 0/26
Treatment 3: 4/24

Outcome 3
Description:
Presence of metastasis in patients with multiple risk factors

Treatment 1 and 2 combined: 4/10
Treatment 3: 2/20

Outcome 4
Description:
Adverse effects

The authors state that none of the patients in this series suffered irreversible systemic toxic effects with either of the drug regimens

Publication details
Authors (year):
Hungerford *et al*. (1997)[124]

Country: UK

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To compare the results of patients with retinoblastoma treated with primary whole-eye EBRT with patients treated with primary lens-sparing EBRT

Study design (brief details):
The case records of a consecutive series of children with retinoblastoma treated at a single hospital were reviewed to compare primary lens-sparing EBRT using a modified Schipper technique administered between 1986 and 1992 with primary whole-eye EBRT administered between 1970 and 1985

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Treatment allocation appeared to depend upon the period during which treatment was received. Patients from 1970 to 1985 were treated with whole-eye EBRT and patients requiring treatment from 1986 onwards received a modified Schipper technique

Sample size calculations:
Not performed

Statistical analyses:
Number (percentage) of eyes was presented for each treatment group. Tests of statistical significance were performed, but information on the test(s) used was not given in the report

Analysis by eyes or participants:
Eyes

Inclusion criteria:
For both treatment groups: eyes had not received prior focal therapy and were assigned to RE group I–III; minimum follow-up of 12 months and complete follow-up data
For patients receiving the lens-sparing technique: patients had an indication for lens-sparing radiotherapy (tumour at or behind equator and unsuitable for focal treatment) because tumour was too close (<5 mm) to optic disc or macula, or too large (>10 mm) for plaque therapy, or tumours were too numerous (more than two tumours for plaque therapy). Lens-sparing radiotherapy was contraindicated as the untreated tumour was anterior to equator, or retinal detachment extended to ora serrata, or vitreous seeding was present

Retinoblastoma classification system used:
RE

Interventions
Treatment 1:
Whole-eye EBRT. If the contralateral eye had been enucleated a direct lateral field was used with beam exit through the enucleated socket. If the contralateral eye was healthy, the radiation portal was positioned at 40 degrees in a superoinferior direction with beam exit through the contralateral maxilla. Where both eyes required EBRT horizontally, opposed lateral fields were used

Dose, number of treatments, etc.:
Dose ranged from 35 Gy in nine or ten fractions to 40 Gy in 20 fractions

Period of treatment:
21 days and 28 days for respective doses

Length of follow-up (mean, SD, range, etc.):
Median 9 years (range 2–17 years)

Adjunctive treatments:
Not reported

Note: The authors report that salvage focal therapy with cryotherapy or brachytherapy was given for recurrences and for persistent or new treatments (details of the number of patients not reported)

continued

Treatment 2:
Lens-sparing EBRT using the modified Schipper technique

Dose, number of treatments, etc.:
40 Gy in 20 equal fractions

Period of treatment:
28 days

Length of follow-up (mean, SD, range, etc.):
Median 3 years (range 1–7 years)

Adjunctive treatments:
Not reported

Note: The authors report that salvage focal therapy with cryotherapy or brachytherapy was given for recurrences and for persistent or new treatments (details of the number of patients not reported)

Participants
Number of participants allocated:
Total (*n*): 155
Treatment 1 (*n*): 102
Treatment 2 (*n*): 53

Number of eyes:
Total (*n*): 201
Treatment 1 (*n*): 139
Treatment 2 (*n*): 62

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not applicable (complete data was an inclusion criterion)

Age of participants:
Total: not reported

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): not reported

Baseline tumour characteristics: Retino classification (RE):
Total (*n*): group I = 34, group II = 88, group III = 79
Treatment 1 (*n*): group I = 16, group II = 55,group III = 68
Treatment 2 (*n*): group I = 18, group II = 33, group III = 11

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results

Outcome 1
Description:
Local tumour control, defined as the number of eyes that did not require enucleation for each treatment group

Treatment 1: overall: 118/139 (85%), group I = 16/16 (100%), group II = 46/55 (84%), group III = 56/68 (82%)
Treatment 2: overall: 57/62 (92%), group I = 18/18 (100%), group II = 29/33 (88%), group III =10/11 (91%)

Note: The results are presented for lens-sparing and whole-eye techniques including focal salvage therapy

Outcome 2
Description:
Number of eyes with new anterior tumours (percentage)

Treatment 1: 2/139 (1.4%)
Treatment 2: 12/62 (19%)

The development of new tumours was significantly lower in patients treated with whole-eye EBRT compared with the lens-sparing technique ($p = 0.001$)

Note: The authors reported that new tumours developed in 13 eyes treated with the lens-sparing technique, 12 of which were located anterior to the equator and were therefore in the low-dose area of radiotherapy field

continued

Outcome 3
Description:
Number of cataracts in eyes retained (i.e. those not enucleated) (median follow-up 35 months)

Treatment 1: 118/118 (100%)
Treatment 2: 0/57 (0%)

The development of a cataract was significantly lower in patients treated with lens-sparing EBRT ($p < 0.0001$)

Publication details
Author (year):
Hungerford (2004)[106]

Country: UK

Type of publication (full paper, abstract):
Conference presentation (slides)

Study design
Authors' objective:
To compare the success rates of primary chemotherapy and radiotherapy

Study design (brief details):
Retrospective observational comparison of: success rate of primary chemotherapy versus radiation alone; overall success rate of primary treatment plus salvage therapy; number and type of salvage treatments required; success rate of salvage. It is not clear where the patients in the study came from, or whether they came from one clinic or more than one

Retrospective/prospective:
Retrospective

How were patients allocated to their treatment group:
Not reported

Sample size calculations:
Not reported

Statistical analyses:
No statistical comparisons between treatment groups

Analysis by eyes or participants:
Eyes

Inclusion criteria:
Genetic retinoblastoma (bilateral or unilateral with family history), diagnosed at less than 1 year classified as RE group I–III

Retinoblastoma classification system used:
RE

Interventions
Treatment 1:
Systemic chemotherapy

Dose, number of treatments, etc.:
Not reported

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median 36 months (range 12–73 months)

Adjunctive treatments:
None

Treatment 2:
Lens-sparing EBRT

Dose, number of treatments. etc.
Not reported

continued

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median 93 months (range 30–193 months)

Adjunctive treatments:
None

Participants
Number of participants allocated:
Total (*n*): 85
Treatment 1 (*n*): 39
Treatment 2 (*n*): 46

Number of eyes:
Total (*n*): 110
Treatment 1 (*n*): 49
Treatment 2 (*n*): 61

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported

Age of participants:
Total: not reported

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 85 bilateral or hereditary

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): all 85 in RE group I–III

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Local tumour control (treatment success) with primary treatment only

Treatment 1: 14/49 (29%)
Treatment 2: 32/61 (53%)

Outcome 2
Description:
Local tumour control with primary and salvage treatment

Treatment 1: 46/49 (94%)
Treatment 2: 59/61 (96%)

Outcome 3
Description:
Mean number of salvage treatments (total, RE group I, RE group II, RE group III)

Treatment 1: 2.94, 3.6, 2.6, 2.5
Treatment 2: 2.14, 2.3, 2.1, 2.0

Outcome 4
Description:
Overall success rate of salvage treatment (total, RE group I, RE group II, RE group III)

Treatment 1: 32/35 (91%), 80%, 100%, 93%
Treatment 2: 27/29 (93%), 100%, 92%, 80%

continued

Outcome 5
Description:
Reasons for failure of primary treatment (resistant tumour, new tumour, local relapse, vitreous relapse)

Treatment 1: 1/49, 24/49, 5/49, 5/49
Treatment 2: 0/61, 26/61, 2/61, 1/61

Publication details
Authors (year):
Kaste *et al*. (1997)[114]

Country: USA

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To determine the effects of enucleation, irradiation, and age at diagnosis on bony orbital growth in long-term survivors of retinoblastoma using CT

Study design (brief details):
Over a 30-year period a total of 160 long-term retinoblastoma survivors (with at least 5 years postdiagnosis) had received treatment for retinoblastoma at a single clinic. Of these patients, 54 had returned for a follow-up visit during the duration of this study and agreed to undergo orbital CT imaging with the above objective in mind

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not explicitly stated, although is likely to be as per hospital protocol

Sample size calculations:
Not reported

Statistical analyses:
Paired *t*-tests and ANOVA were used to compare differences between treatment modalities

Analysis by eyes or participants:
Participants
Inclusion criteria:
Long-term survivors of retinoblastoma (at least 5 years postdiagnosis) who had attended the hospital for a follow-up visit during the duration of the study, and gave consent to undergo orbital CT imaging

Retinoblastoma classification system used:
Not reported

Note: The authors also reported on the impact of age of diagnosis on orbital development. However, this outcome is not of interest to this review and has not been extracted

Interventions

Intervention group 1: patients with unilateral retinoblastoma
Treatment 1:
Enucleation. All patients were given an implant at the time of surgery. The size of implant ranged from 12 to 22 mm in diameter

Dose, number of treatments, etc.:
Not applicable

Period of treatment:
Not applicable

Length of follow-up (mean, SD, range, etc.):
Median follow-up was 7.5 years (range 4.9–25.8 years) (for both treatment groups combined)

Adjunctive treatments:
None

continued

Treatment 2:
Enucleation and EBRT. All patients were given an implant at the time of surgery. The size of implant ranged from 12 to 22 mm in diameter. EBRT was administered after enucleation using anterior fields, lateral fields or combined anterior and lateral fields. Radiation was delivered after enucleation in all but one case

Dose, number of treatments, etc.:
EBRT was given in doses of 22.5–44 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median follow-up was 7.5 years (range 4.9–25.8 years) (for both treatment groups combined)

Adjunctive treatments:
Not reported

Intervention group 2: patients with bilateral retinoblastoma
Treatment 1:
Unilateral enucleation and contralateral EBRT. All patients were given an implant at the time of surgery. The size of implant ranged from 12 to 22 mm in diameter. EBRT was administered after enucleation using anterior fields, lateral fields or combined anterior and lateral fields

Dose, number of treatments, etc.:
EBRT was given in doses of 22.5–44 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median follow-up was 7.5 years (range 4.9–25.8 years) (for all treatment groups combined)

Adjunctive treatments:
Not reported

Treatment 2:
Bilateral EBRT delivered using anterior fields, lateral fields or combined anterior and lateral fields

Dose, number of treatments, etc.:
EBRT was given in doses of 22.5–44 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median follow-up was 7.5 years (range 4.9–25.8 years) (for all treatment groups combined)

Adjunctive treatments:
Not reported

Treatment 3:
Bilateral enucleation and bilateral EBRT. All patients were given an implant at the time of surgery. The size of implant ranged from 12 to 22 mm in diameter. EBRT was administered after enucleation using anterior fields, lateral fields or combined anterior and lateral fields

Dose, number of treatments, etc.:
EBRT was given in doses of 22.5–44 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median follow-up was 7.5 years (range 4.9–25.8 years) (for all treatment groups combined)

Adjunctive treatments:
Not reported

Treatment 4:
Unilateral enucleation and bilateral EBRT. All patients were given an implant at the time of surgery. The size of implant ranged from 12 to 22 mm in diameter. EBRT was administered after enucleation using anterior fields, lateral fields or combined anterior and lateral fields

Dose, number of treatments, etc.:
EBRT was given in doses of 22.5–44 Gy

continued

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median follow-up was 7.5 years (range 4.9–25.8 years) (for all treatment groups combined)

Adjunctive treatments:
Not reported

Participants
Number of participants allocated:
Total (*n*): 54

Intervention group 1 (unilateral disease): 26
Treatment 1 (*n*): 24
Treatment 2 (n): 2

Intervention group 2 (bilateral disease): 27
Treatment 1 (*n*): 18 (1 patient was excluded from orbital configuration measurements owing to extensive postoperative and postirradiation changes related to recurrent disease)
Treatment 2 (*n*): 3
Treatment 3 (*n*): 2
Treatment 4 (*n*): 4

Number of eyes:
Total (*n*): 82

Intervention group 1: 26
Treatment 1 (*n*): 24
Treatment 2 (*n*): 2

Intervention group 2: 56
Treatment 1 (*n*): not reported
Treatment 2 (*n*): not reported
Treatment 3 (*n*): not reported
Treatment 4 (*n*): not reported

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported

Age of participants:
Total: median age at diagnosis was 13 months (range 1 day to 6.9 years); median age at time of follow-up was 13 years (range 5.2–28.8 years)
Unilateral disease: 9 aged ≤ 1 year and 17 aged > 1 year at diagnosis
Bilateral disease: 17 aged ≤ 1 year and 10 aged > 1 year at diagnosis

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 26 unilateral and 28 bilateral
Intervention group 1: 26 unilateral
Intervention group 2: 28 bilateral

Baseline tumour characteristics: Retinoblastoma classification:
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Enhanced CT imaging was performed on both orbits in each patient. Orbital volumes were calculated using the transverse and anteroposterior orbital dimensions. Orbital volume was defined as the difference in volume between the two orbits in each case and presented as median volume difference and range (cm^3)

continued

Intervention group 1:
Treatment 1 (n = 24): median = 1.5 cm^3 (range 0–9.6 cm^3)
Treatment 2 (n = 2): median = 1.4 cm^3 (range 0.2–1.5 cm^3)

Intervention group 2:
Treatment 1 (n = 18): median = 2 cm^3 (range 0.0–6.1 cm^3)
Treatment 2 (n = 3): median = 0.3 cm^3 (range 0.0–0.7 cm^3)
Treatment 3 (n = 2): median = 4.9 cm^3 (range 0.2–9.6 cm^3)
Treatment 4 (n = 4): median = 2.5 cm^3 (range 0.3–4.12 cm^3)

The authors report that in patients with unilateral disease (n = 26) the effects of enucleation and high-dose irradiation (>35 Gy) were significant regardless of age (p-value not given)
Sufficient data were available to assess the effects of type of treatment and age at diagnosis on orbital volume for patients with one eye enucleated and the other untreated (24 patients with unilateral disease), and patients with one eye enucleated and the other irradiated (18 patients with bilateral disease). In patients with one eye enucleated and the other untreated orbital volume was significantly larger in those patients who underwent enucleation (p = 0.014). The orbital volumes did not differ significantly in patients who had one eye enucleated and the other irradiated (p = 0.13), but high-dose irradiation (>35 Gy) significantly affected orbital development (p = 0.022)

Publication details
Authors (year):
Lee *et al*. (2003)[129]

Country: USA

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To determine the frequency and timing of new intraocular tumours in children with hereditary retinoblastoma who were initially treated with systemic carboplatin

Study design (brief details):
This was a retrospective, non-comparative case series. Children diagnosed with bilateral retinoblastoma who were treated with systemic carboplatin chemotherapy at two hospitals from 1994 to 2000 were reviewed with the above objective in mind. Two treatment groups were identified, consisting of those who received carboplatin and those that received carboplatin and radiation (EBRT or brachytherapy)

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Patients were given treatment according to hospital protocol, and after obtaining consent from their family. Patients were allocated to treatment group according to need relating to the severity of disease and treatment response. The authors report that patients who had a reduction in tumour size following initial intravenous carboplatin were given subsequent chemotherapy until the tumour was small enough to be treated by focal therapy. Tumours that did not respond to treatment were given no further carboplatin and alternative treatment methods were used

Sample size calculations:
Not reported

Statistical analyses:
For the treatment comparison of interest to this review, no tests of statistical significance were used to compare the treatment groups. The authors determined the likelihood that an eye would develop a new tumour after initial treatment with systemic carboplatin using Kaplan–Meier analysis. Eyes were censored after enucleation, EBRT, plaque or end of follow-up. Wilcoxon tests were used to compare data sets

Analysis by eyes or participants:
Eyes

Inclusion criteria:
Patients were eligible for inclusion if they had bilateral retinoblastoma. Eyes were excluded if they received EBRT as initial treatment, were enucleated within 1 month of receiving initial carboplatin treatment, or had less than 1 year of follow-up data, or had vitreous seeding at presentation of disease

Retinoblastoma classification system used:
Not reported

continued

Interventions
Treatment 1:
Carboplatin only

Dose, number of treatments, etc.:
Patients received intravenous carboplatin at 18.7 mg kg^{-1} for children who weighed <12 kg, and 560 mg m^{-2} for children who weighed >12 kg. The mean number of treatments was 2.4 per patient

Period of treatment:
The period of treatment is not given in the report. However, patients who had a reduction in tumour size were given subsequent chemotherapy until the tumour was small enough to be treated with focal therapy. If tumours were unresponsive to treatment, no further carboplatin was given and alternative treatment methods were used. The earliest treatment was given at 2 weeks of life and the latest at 30 months

Length of follow-up (mean, SD, range, etc.):
Mean follow-up was 35.7 months (range 12–81 months) (for both treatment groups combined). All patients were at least 1 year of age at last follow-up examination, and most were more than 2 years of age. Examinations were performed 3–4 weeks after initial treatment with carboplatin

Adjunctive treatments:
Periocular carboplatin was given in addition to systemic carboplatin in four patients. The authors report that this subset of patients was treated with carboplatin and focal treatments. The local treatments used included cryotherapy and 810-nm photocoagulation. The number of patients who were given local therapy and how many patients received which local therapy is not given in the report

Treatment 2:
Systemic carboplatin was given as the initial treatment followed by radiation (EBRT or brachytherapy)
EBRT was delivered using a lateral lens-sparing portal, and brachytherapy was delivered using ^{125}I plaques

Dose, number of treatments, etc.:
Patients received intravenous carboplatin at 18.7 mg kg^{-1} for children who weighed <12 kg, and 560 mg m^{-2} for children who weighed >12 kg. The mean number of treatments was 2.7 per patient
Dosage and number of treatments for EBRT and brachytherapy are not given in the report

Period of treatment:
The period of treatment is not given in the report. However, patients who had a reduction in tumour size were given subsequent chemotherapy until the tumour was small enough to be treated with focal therapy. If tumours were unresponsive to treatment, no further carboplatin was given and alternative treatment methods were used
The mean time from initiation of treatment with carboplatin to radiation was 8.3 months, and the average age of treatment with EBRT was 14.6 months (range 4.4–48.2 months). Most children who received radiation therapy were treated after 1 year of age, and most patients who were given radiation therapy were given EBRT
The earliest treatment with carboplatin was given at 2 weeks of life and the latest at 30 months

Length of follow-up (mean, SD, range, etc.):
Mean follow-up was 35.7 months (range 12–81 months) (for both groups combined). All patients were at least 1 year of age at last follow-up examination, and most were more than 2 years of age. Examinations were performed 3–4 weeks after initial treatment with carboplatin

Adjunctive treatments:
25 eyes received EBRT (2 eyes before 6 months of age, 9 eyes between 6 and 12 months, and 15 eyes after 1 year of age) and 7 received brachytherapy (2 eyes before 6 months of age, 4 eyes between 6 and 12 months, and 1 eye after 1 year of age) and 1 eye was given periocular carboplatin in addition to systemic carboplatin. The authors report that this subset of patients was treated with carboplatin and eventual radiation (EBRT or brachytherapy). It is not clear whether patients in this subset were given focal therapy, other than radiation, before eventual radiation therapy

Participants
Number of participants allocated:
Total (*n*): 34
Treatment 1 (*n*): 13
Treatment 2 (*n*): 21 (the authors report that 15 patients received EBRT and 6 received brachytherapy)

Number of eyes:
Total (*n*): 57
Treatment 1 (*n*): 25
Treatment 2 (*n*): 32

continued

Number of tumours:
Total (*n*): 165 (mean number of tumours per eye 2.9)
Treatment 1 (*n*): 76 (3 per eye)
Treatment 2 (*n*): 89 (2.8 per eye)

Dropouts:
Total (*n*): not applicable

Age of participants (at diagnosis):
Total: 6.4 months (range 0–29 months)
Treatment 1: 7.8 months (range 0–29 months)
Treatment 2: 5.2 months (range 0–13.7 months)

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): all 34 patients had bilateral and hereditary retinoblastoma

Baseline tumour characteristics: Retinoblastoma classification (RE or equivalent):
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): the authors state that patients presenting with vitreous seeding were excluded from the study; however, it is reported that one patient had vitreous seeding at presentation. It is not clear whether this patent was included in the analysis, or which treatment was given

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
The number of eyes that develop new tumours after treatment with carboplatin and radiation, and the number of new tumours (mean) per eye

Treatment 1: 14/25 (56%); 34 new tumours (mean per eye = 1.4)
Treatment 2: 13/32 (41%); 29 new tumours (mean per eye = 0.9)

Subgroup analysis of outcome 1
Description:
The number of eyes that developed new tumours according to age at initial carboplatin and treatment method

Treatment 1: <6 months: 11/15 (73%), >6 months: 3/10 (30%)
Treatment 2: <6 months: 10/20 (50%), >6 months: 3/12 (25%)

Kaplan–Meier analysis was performed separately on eyes treated before and after 6 months of age. The probability of an eye remaining tumour free after initial carboplatin treatment was 69% in children treated after the age of 6 months compared with 40% in children treated before the age of 6 months ($p = 0.0182$)

Outcome 2
Description:
The number of eyes eventually requiring enucleation

Treatment 1: 4/25
Treatment 2: 6/32

The authors reported that the mean age at enucleation was 23.6 months and 32.2 months for patients in treatment groups 1 and 2, respectively

Publication details
Authors (year):
Lee *et al*. (2000)[116]

Country: UK

Type of publication (full paper, abstract):
Full paper

continued

Study design

Authors' objective:
To determine significant factors influencing the exposure of primary orbital implants in patients with retinoblastoma

Study design (brief details):
Records of consecutive patients who had undergone enucleation between January 1993 and December 1997 were reviewed for exposure of their orbital implants

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
For allocation to the treated or untreated group clinical indications for treatment with chemotherapy only are provided; most patients with bilateral disease received first line chemotherapy following enucleation of the fellow eye; chemotherapy was administered after a report of adverse findings in the enucleation specimen; and second line chemotherapy was initiated in a number of situations including vitreous relapse in an eye following first line chemotherapy

Sample size calculations:
None reported

Statistical analyses:
For the outcomes of interest the rate of orbital implant exposures was reported

Analysis by eyes or participants:
Eyes and participants

Inclusion criteria:
Patients treated at the Ocular Oncology Service (at St Bartholomew's Hospital and Moorfield Eye Hospital) from January 1993 to December 1997 with a minimum of 3 months' follow-up were eligible for inclusion

Retinoblastoma classification system used:
None

Interventions

Treatment 1:
Untreated sockets: patients who, following enucleation, had undergone cryotherapy, thermotherapy or brachytherapy or who had orbital implant exposure develop before their chemotherapy or radiotherapy

Dose, number of treatments, etc.:
Not stated

Period of treatment:
Not stated

Length of follow-up (mean, SD, range, etc.):
Median 21.6 months (range 3–55 months) following enucleation (for both treatment groups combined)

Adjunctive treatments:
See above

Treatment 2
Treated sockets: patients who, following enucleation, had received chemotherapy and/or EBRT at a dose of 40–50 Gy before or at the time of exposure

Dose, number of treatments, etc.:
Vincristine, etoposide and carboplatin for first and second line chemotherapy
EBRT: whole-eye or lens-sparing technique, 40–50 Gy

Period of treatment:
Firstline chemotherapy: six to eight courses at 3-week intervals; second line chemotherapy: four courses of adjuvant treatment

Length of follow-up (mean, SD, range, etc.):
Median 21.6 months (range 3–55 months) following enucleation (for both treatment groups combined)

Adjunctive treatments:
Brachytherapy (8 eyes)

Participants

Number of participants allocated:
Total (*n*): 109 (107 included in the analysis)
Treatment 1 (*n*): 57 included in the analysis
Treatment 2 (*n*): 50 included in the analysis

continued

Number of eyes:
Total (*n*): 110 sockets (108 included in the analysis)
Treatment 1 (*n*): 57
Treatment 2 (*n*): 51

Number of tumours:
Total (*n*): not applicable

Dropouts:
Total (*n*): two patients with secondary exposure of the implants due to orbital retinoblastoma were excluded from the analysis

Age of participants:
Total: median age at diagnosis 19 months (range birth to 136 months); median age at enucleation 24.0 months (range 1–154 months)

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): unilateral sporadic 70, unilateral familial 2, bilateral sporadic 33, bilateral familial 3

Baseline tumour characteristics: Retinoblastoma classification (RE or equivalent):
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (n): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Rate of exposure of orbital implants

Treatment 1: 12/57 (20%)
Treatment 2: 18/51 (35%)

Further data are reported in the paper examining the effects on rate of exposure of implant type and covering, age at enucleation, gender, diagnosis, surgeon, implant size, radiotherapy and chemotherapy

Publication details
Authors (year):
Merrill *et al*. (1996)[110]

Country: USA

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To determine the incidence of new and recurrent tumours in patients with germinal retinoblastoma treated with EBRT or focal therapy (laser therapy, cryotherapy or brachytherapy)

Study design (brief details):
The medical charts of all patients with hereditary retinoblastoma who received EBRT or focal therapy (photocoagulation, cryotherapy or brachytherapy) treatment at the Duke University Eye Clinic from 1983 to 1993 were reviewed to determine whether treatment was associated with the occurrence of new and recurrent tumours

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not explicitly stated, although is likely to be according to the treatment that patients actually received as per hospital protocol

Sample size calculations:
Not performed

continued

Statistical analyses:
χ^2 tests and Student's *t*-test were used to compare treatment groups

Analysis by eyes or participants:
Eyes

Inclusion criteria:
Patients with germinal retinoblastoma (bilateral disease or positive family history) with follow-up data of 2 years or more were eligible for inclusion
One patient with one eye that had been initially treated with both EBRT and cryotherapy was excluded
Eyes that were RE group V were excluded

Retinoblastoma classification system used:
RE

Interventions
Treatment 1:
EBRT: all eyes were irradiated with a 4-MV linear accelerator. For patients who had one eye irradiated a lateral beam delivering 80–85% of the dose and an anterior beam delivering 15–25% of the dose were used. For patients requiring treatment to both eyes three beams were used: two parallel opposed lateral beams delivering the dose to both globes and a single anterior beam with lead alloy blocks to shield the bridge of the nose. Rigid immobilisation was ensured using a plaster or thermoplastic head holder, and anaesthesia

Dose, number of treatments, etc.:
The radiation dose was 43.8 Gy with a mean dose per fraction of 1.84 Gy once daily for 5 days per week

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Not reported

Adjunctive treatments:
Three patients received postirradiation vincristine/cyclophosphamide. One patient received vincristine/cyclophosphamide plus intrathecal methotrexate, ara-C and hydrocortisone as an adjunct to enucleation and cryotherapy owing to trilateral retinoblastoma

Treatment 2:
Cryotherapy using a triple-thaw technique, photocoagulation using a diode laser or brachytherapy using ^{125}I plaques

Dose, number of treatments, etc.:
^{125}I plaque brachytherapy using a dose of 43.26 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Not reported

Adjunctive treatments:
Four patients received both EBRT and focal therapy

Participants
Number of participants allocated:
Total (*n*): 17
Treatment 1 (*n*): 12
Treatment 2 (*n*): 9

Note: The total number of patients stated in the paper does not correspond with the number stated for the two treatment groups.

Number of eyes:
Total (*n*): 24
Treatment 1 (*n*): 15
Treatment 2 (*n*): 9 (7 cryotherapy, 1 photocoagulation, 1 brachytherapy)

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported

continued

Age of participants:
Total: not reported
Treatment 1: mean 6 months, median 4.5 months (range 0.3–18 months)
Treatment 2: mean 11.3 months, median 11 months (range 1–29 months)

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): all 17 patients had hereditary retinoblastoma
Treatment 1 (*n*): 12 hereditary (1 with trilateral)
Treatment 2 (*n*): 9 hereditary

Baseline tumour characteristics: Retinoblastoma classification
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*) not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
The number of patients (percentage) with a new tumour, defined as a tumour appearing at the distant site unrelated to any prior tumour

Treatment 1: 1/15 (7%)
Treatment 2: 1/9 (11%) (patient had received cryotherapy)

No significant difference between treatment modalities (*p*-value not reported)

Outcome 2
Description:
The number of patients (percentage) with a recurrent tumour, defined as the regrowth of a tumour within, or next to the scar of the regressed tumour

Treatment 1: 1/15 (7%)
Treatment 2: 1/9 (11%) (patient had received cryotherapy)

No significant difference between treatment modalities (*p*-value not reported)

Note: One eye contained one of the new tumours and one of the recurrent tumours. This patient had received initial adjuvant chemotherapy

Publication details
Authors (year):
Messmer *et al*. (1990)[112]

Country: Germany

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To evaluate the incidence, location and latency of treatment failure (defined as development of new and recurrent tumour foci in the eye) in patients with hereditary retinoblastoma treated with EBRT compared with patients treated with local treatment

Study design (brief details):
An analysis of primarily computerised files of 200 patients with hereditary retinoblastoma seen at a single centre since 1960 was performed. All cases before 1982 had been entered retrospectively into the file; since 1983 all data entry was done prospectively. The percentage of eyes developing new or recurring tumours during a 5-year follow-up period was compared for local therapy and EBRT

Retrospective/prospective:
Retrospective and prospective

continued

How patients were allocated to their treatment group:
Not explicitly stated, although it is likely to be according to the treatment received as per hospital protocol. The authors stated that local treatment tended to be used in cases with small tumours not located close to the fovea or the disc and with no retinal detachment or vitreous seeding. EBRT tended to be used for larger and centrally located tumours as well as some cases with vitreous seeding and retinal detachment

Sample size calculations:
Not performed

Statistical analyses:
χ^2 test for binomial data; life tables for time to event data (to adjust for different follow-up times) were generated using Mantel–Breslow procedures and tested according to Breslow and Mantel-Cox

Analysis by eyes or participants:
Eyes

Inclusion criteria:
Consecutive patients at risk of developing multiple tumours (patients with multifocal disease or unilateral disease with first degree relative with the disease) were included
Patients who had received chemotherapy before the occurrence of new or recurrent tumours, and patients who had been partly treated elsewhere or for whom there was poor documentation were excluded
Local therapy: all eyes primarily treated with local therapy (photocoagulation, cryocoagulation or plaque therapy where no EBRT had been performed within 4 weeks of initiation of local therapy) since 1960 were included
EBRT: only eyes that were treated with megavoltage therapy (1974–1988) were included. Eyes with total retinal detachment diffuse vitreous seeding or tumours larger than half of the retina were excluded

Retinoblastoma classification system used:
Not reported

Interventions
Treatment 1:
Patients receiving local therapy were exclusively treated with photocoagulation, cryocoagulation or plaque therapy before the development of recurrences

Dose, number of treatments, etc.:
Plaque therapy: ruthenium plaques (^{106}Ru) were used for 6 tumours and cobalt plaques (^{60}Co) for 4 tumours. A radiation dose of 40 Gy was applied to the apex of the tumour in 70% of cases

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Mean 7.1 years (median 5.8 years, range 0–23 years) (for combined treatment groups)

Adjunctive treatments:
Cases in which secondary or additional EBRT was given to treat new or recurrent tumours, or where secondary chemotherapy was used, were classified as lost to follow-up from the beginning of the new course of treatment in relation to further evaluation of new and recurrent tumours

Treatment 2:
EBRT delivered using megavoltage therapy (1974–1988) with a subgroup of eyes treated with a beam alignment technique adapted from the one described by Schipper (1980)

Dose, number of treatments, etc.:
Radiation doses of 40 and 50 Gy were distributed equally between both subgroups. 81% of cases received a total radiation dose between 37 and 51 Gy

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Mean 7.1 years (median 5.8 years, range 0–23 years) (for combined treatment groups)

Adjunctive treatments:
Cases in which secondary or additional EBRT was received to treat new or recurrent tumours, or secondary chemotherapy was used, were classified as lost to follow-up from the beginning of the new course of treatment in relation to further evaluation of new and recurrent tumours

continued

Participants
Number of participants allocated:
Total (*n*): 200
Treatment 1 (*n*): not reported (an 'unselected subseries' of 77 patients was used for the analysis)
Treatment 2 (*n*): not reported

Number of eyes:
Total (n): 229
Treatment 1 (*n*): 102 (an 'unselected subseries' of 83 eyes was used for the analysis)
Treatment 2 (*n*): 127

Number of tumours:
Total (*n*): not reported
Treatment 1 (*n*): total number of tumours in this group is unclear. Analysis was carried out on an 'unselected subseries' of 106 tumours (cryocoagulation 27, photocoagulation 69, plaque therapy 10)
Treatment 2 (*n*): not reported

Dropouts:
Total (*n*): not reported (not applicable)

Age of participants:
Total: not reported

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): bilateral 196/200, unilateral 4/200, all cases were hereditary

Baseline tumour characteristics: Retinoblastoma classification:
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not explicitly stated. Eyes with diffuse vitreous seeding were excluded from the primary EBRT group and also (implied) from the local therapy group

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Average number of applications of local therapy necessary to 'sterilise' the tumour (the authors do not specify what they mean by sterilise)

Treatment 1: cryocoagulation ($n = 27$ tumours) average 1.6 applications; photocoagulation ($n = 69$ tumours) average 2.6 applications; plaque therapy ($n = 10$ tumours) average 1 application ($p = 0.0039$ cryocoagulation vs photocoagulation)
Treatment 2: not applicable

Outcome 2
Description:
Percentage of eyes developing new tumours during a 5-year follow-up period. (New tumours were defined as tumours that had no relationship to pre-existing tumours and were observed more than 4 weeks after the initiation of therapy)

Treatment 1: 20%
Treatment 2: 27%

Note: The *n* value or denominator is not specified for either treatment group. It is unclear whether the local therapy group included all 102 eyes or only the subsample of 83 eyes for this outcome or the other relevant outcomes below

Outcome 3
Description:
Time interval (latency) between the initiation of therapy and the detection of a new tumour

Treatment 1: median 4 months
Treatment 2: median 9 months

The time interval between initiation of therapy and detection of new tumour was significantly longer in treatment group 3 than group 1 ($p = 0.02$)

continued

Outcome 4
Description:
Percentage of eyes developing recurrent tumours during a 5-year follow-up period. (Recurrent tumours were defined as tumours that developed from previously successfully treated areas, i.e. had been described as inactivated)

Treatment 1: 26% (photocoagulation 28%, cryocoagulation 33%, plaque therapy 0%. In 50% of the plaque therapy cases additional photocoagulation or cryocoagulation was applied to tumours with mixed regression patterns)
Treatment 2: 28%

Note: The *n* value or denominator is not specified for either treatment group

Outcome 5
Description:
Percentage of eyes developing new and recurrent tumours

Treatment 1: 35%
Treatment 2: 44%

Note: The *n* value or denominator is not specified for either treatment group

Outcome 6
Description:
Percentage of eyes developing new and recurrent tumours in the EBRT group receiving doses of 49–51 Gy and 37–41 Gy

Treatment 1: not applicable
Treatment 2: 49–51 Gy ($n = 40$) 22% versus 37–41 Gy ($n = 71$) 49%

Note: The denominator is not specified for either treatment group

Outcome 7
Description:
Percentage of eyes developing new and recurrent tumours using the bean alignment technique described by Schipper compared with alignment using the outer bony canthus

Treatment 1: not applicable
Treatment 2: Schipper method ($n = 54$) 22% versus lateral canthus ($n = 73$) 48%

Note: The denominator is not specified for either treatment group

Publication details
Authors (year):
Mohr *et al*. (1990)[120]

Country: Germany

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To study the influence of enucleation bulbi and radiation on subsequent midfacial growth inhibition

Study design (brief details):
99 patients who had been treated at a single centre for bilateral retinoblastoma were reviewed after 15.5 years. 15 untreated facial halves were compared with facial halves of patients who underwent enucleation, radiation or enucleation plus radiation. Some patients received bilateral treatment

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not reported

Sample size calculations:
None stated

Statistical analyses:
Average value (probably mean but not explicitly stated) for growth inhibition reported, statistical significance tested for (but not stated how); 46 clinical parameters were analysed

continued

Analysis by eyes or participants:
Facial halves

Inclusion criteria:
Only patients who had received a radiation dose between 36 and 51 Gy were analysed. No further information reported

Retinoblastoma classification system used:
Not reported

Interventions
Treatment 1:
Local therapy (cryotherapy or laser techniques)

Dose, number of treatments, etc.:
Not reported

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
15.5 years (for all groups combined)

Adjunctive treatments:
Not reported

Note: Specifically one eye was treated

Treatment 2:
Enucleation

Dose, number of treatments, etc.:
Not reported

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
15.5 years (for all groups combined)

Adjunctive treatments:
Not reported

Treatment 3:
Radiotherapy

Dose, number of treatments, etc.:
Not reported

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
15.5 years (for all groups combined)

Adjunctive treatments:
Not reported

Treatment 4:
Enucleation and radiotherapy

Dose, number of treatments, etc.:
Dose and number of treatments not reported. Patients were treated bilaterally

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
15.5 years (for all groups combined)

Adjunctive treatments:
Not reported

continued

Participants
Number of participants allocated:
Total (*n*): 99

Number of eyes:
Total (*n*): 169 facial halves
Treatment 1 (*n*): 15 facial halves
Treatment 2 (*n*): 67 facial halves
Treatment 3 (*n*): 68 facial halves
Treatment 4 (*n*): 19 facial halves

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): exact number unclear (number in tables and text do not add up)

Age of participants:
Total: not reported

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 99 bilateral

Baseline tumour characteristics: Retinoblastoma classification (RE or equivalent):
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Total midface growth inhibition based on the evaluation of six midfacial regions (on a rating scale of 0 for no inhibition to 5 for extreme inhibition)

Treatment 1: 0.27
Treatment 2: 1.21
Treatment 3: 2.26
Treatment 4: 3.53

Publication details
Authors (year):
Moll *et al.* (2001)[117]

Country: The Netherlands

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To evaluate the influence of age at receiving EBRT on the occurrence of SPTs inside and outside the radiation field in patients with hereditary retinoblastoma

Study design (brief details):
A Dutch retinoblastoma register was developed using hospital records to identify all hereditary retinoblastoma patients who were born in The Netherlands between 1945 and 1997. Data were obtained on the mode of treatment, age at irradiation, the occurrence and location of SPTs, and survival in 263 patients with hereditary retinoblastoma. Information on SPTs was obtained by different methods depending on whether patients were alive or dead and when they had been born. If deceased, information was obtained from the last treatment physician. Information gathered previously from home visits in 1985 was used for those born before 1970. A detailed history was obtained by interview for patients born after 1970. Clinical and histopathological records confirmed reported SPTs. Incidence of SPTs was compared for those receiving EBRT before 12 months old, after 12 months old and those not receiving EBRT

continued

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not explicitly stated, although is likely to be according to the treatment actually received as per hospital protocol

Sample size calculations:
Not performed

Statistical analyses:
Kaplan–Meier analyses were used to calculate cumulative incidence of SPTs and treatment groups were compared using the Mantel–Cox (log rank) test. Patients with multiple SPTs were counted as one case
Sensitivity analysis was performed based on the definition of SPT proposed by Abramson and Frank,[137] which included defining pineoblastoma as an SPT inside the radiation field. An analysis was also performed with pineoblastoma defined as an SPT outside the radiation field (the authors refer to this as a 'compromise')

Analysis by eyes or participants:
Participants

Inclusion criteria:
Patients were considered to have hereditary retinoblastoma if they had bilateral retinoblastoma, a positive family history of retinoblastoma or a defect in the retinoblastoma gene found in DNA analysis
SPTs were defined according to the Warren and Gates criteria, that is, each of the tumours must present a definite picture of malignancy, each tumour must be distinct and the possibility that an SPT is a metastatic lesion of the primary tumour must be excluded. Pineoblastoma was not classified as an SPT

Retinoblastoma classification system used:
Not reported

Interventions
Treatment 1:
EBRT before 12 months of age (early EBRT). From 1971 all patients were treated with a 6- or 8-MV photon beam in a 20 x 26 mm D-shaped field (Schipper technique)

Dose, number of treatments, etc.:
Radiation dose of 45 Gy delivered in 15 fractions, three fractions per week

Period of treatment:
Not specified, but appears to be 5 weeks

Length of follow-up (mean, SD, range, etc.):
20 years (median 18 years, range 1 month to 48 years) (for both treatment groups combined)

Adjunctive treatments:
Some patients also received chemotherapy

Treatment 2:
EBRT after 12 months of age (late EBRT). From 1971 all patients were treated with a 6- or 8-MV photon beam in a D-shaped field (Schipper technique)

Dose, number of treatments, etc.:
Radiation dose of 45 Gy delivered in 15 fractions, three fractions per week

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
20 years (median 18 years, range 1 month to 48 years) (for both treatment groups combined)

Adjunctive treatments:
Some patients also received chemotherapy

Treatment 3:
No irradiation

Dose, number of treatments, etc.:
Not applicable

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc):
20 years (median 18 years, range 1 month to 48 months) (for both treatment groups combined)

continued

Adjunctive treatments:
Not reported

Participants
Number of participants allocated:
Total (*n*): 263
Treatment 1 (*n*): 128
Treatment 2 (*n*): 55
Treatment 3 (*n*): 80

Number of eyes:
Total (*n*): not reported

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): 4 patients were lost to follow-up

Age of participants:
Total: not reported

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 263 hereditary
Treatment 1 (*n*): 128 hereditary
Treatment 2 (*n*): 55 hereditary
Treatment 3 (*n*): 80 hereditary

Baseline tumour characteristics: Retinoblastoma classification (RE or equivalent):
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Cumulative incidence of SPTs at the age of 25 years determined using Kaplan–Meier curves

Treatment 1: 22% (95% CI 13 to 34%)
Treatment 2: 3% (95% CI 0 to 14%)
Treatment 3: 5% (95% CI 1 to 16%)

Overall $p = 0.001$; difference between early and late EBRT $p = 0.04$

Outcome 2
Description:
Cumulative incidence of SPTs inside the irradiation field at the age of 25 years determined using Kaplan–Meier curves. Tumours were classified as inside the field of radiation if their origin was the eyelids, orbits, periocular sinuses, temporal bones or skin overlying the temporal bone region

Treatment 1: 11% (95% CI 6 to 22%)
Treatment 2: 3% (95% CI 0 to 13%)
Treatment 3: 0% (95% CI 0 to 8%)

Overall $p = 0.03$; difference between early and late EBRT $p = 0.37$

Outcome 3
Description
Cumulative incidence of SPTs outside the irradiation field at the age of 25 years determined using Kaplan–Meier curves. Tumours were classified as outside the field if they occurred in locations such as the thyroid gland, neck or brain

Treatment 1: 11% (95% CI: 6 to 22%)
Treatment 2: 0% (95% CI: 0 to 9%)
Treatment 3: 5% (95% CI: 1 to 16%)

Overall $p = 0.03$; difference between early and late EBRT $p = 0.06$

continued

Sensitivity analysis (a): outcome 1
Description:
Cumulative incidence of SPT at the age of 25 years determined using Kaplan–Meier curves assuming that pineoblastoma is considered an SPT inside the irradiation field, as proposed by Abramson and Frank

Treatment 1: 26% (95% CI 16 to 38%)
Treatment 2: 3% (95% CI 0 to 14%)
Treatment 3: 6% (95% CI 2 to 18%)

Overall $p = 0.003$; difference between early and late EBRT $p = 0.01$

Sensitivity analysis (a): outcome 2
Description:
Cumulative incidence of SPTs inside the irradiation field at the age of 25 years determined using Kaplan-Meier curves assuming that pineoblastoma is considered an SPT inside the irradiation field, as proposed by Abramson and Frank

Treatment 1: 20% (95% CI 12 to 32%)
Treatment 2: 3% (95% CI 0 to 14%)
Treatment 3: 2% (95% CI 0 to 13%)

Overall $p = 0.004$; difference between early and late EBRT $p = 0.04$

Sensitivity analysis (a): outcome 3
Description:
Cumulative incidence of SPTs outside the irradiation field at the age of 25 years determined using Kaplan–Meier curves assuming that pineoblastoma is considered an SPT inside the irradiation field, as proposed by Abramson and Frank

Treatment 1: 7% (95% CI 3 to 17%)
Treatment 2: 0% (95% CI 0 to 9%)
Treatment 3: 5% (95% CI 1 to 16%)

Overall $p = 0.06$; difference between early and late EBRT $p = 0.12$

Sensitivity analysis (b): outcome 2
Description:
Cumulative incidence of SPT inside the irradiation field at the age of 25 years determined using Kaplan–Meier curves assuming that pineoblastoma is an SPT outside the field of radiation

Treatment 1: 15% (95% CI 8 to 16%)
Treatment 2: 3% (95% CI 0 to 14%)
Treatment 3: 0% (95% CI 0 to 18%)

Overall $p = 0.009$; difference between early and late EBRT $p = 0.18$

Sensitivity analysis (b): outcome 3
Description:
Cumulative incidence of SPT outside the irradiation field at the age of 25 years determined using Kaplan–Meier curves assuming that pineoblastoma is an SPT outside the field of radiation

Treatment 1: 13% (95% CI 6 to 23%)
Treatment 2: 0% (95% CI 0 to 9%)
Treatment 3: 6% (95% CI 2 to 18%)

Overall $p = 0.01$; difference between early and late EBRT $p = 0.02$

Note: Some of the figures quoted by the authors for outcomes 2 and 3 do not equal the figures reported for the corresponding total incidence of SPTs reported for outcome 1. The discrepancies were: (i) when using the authors' definition of an SPT, the total number of SPTs identified was 30, but the authors report on the location of 29 (14 inside the field of radiation and 15 outside); (ii) when using the Abramson and Frank definition of an SPT, the total number of SPTs identified was 35, but the authors report on the location of 37 (25 inside the field of radiation and 12 outside)

Outcome 4:
Description:
Total number of SPTs (inside and outside the irradiation field)

Treatment 1: 24/128
Treatment 2: 7/55
Treatment 3: 3/80

continued

Outcome 5
Description:
Total number of SPTs inside the irradiation field

Treatment 1: 10/24
Treatment 2: 4/7
Treatment 3: 0/3

Outcome 6
Description:
Total number of SPTs outside the irradiation field

Treatment 1: 14/24
Treatment 2: 3/7
Treatment 3: 3/3 (hypothetical irradiation field)

Publication details
Authors (year):
Pasqualini *et al*. (1991)[119]

Countries: Argentina and USA

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To investigate growth, pubertal development and endocrine function in children who were given different modes of treatment (radiotherapy vs no radiotherapy or retinal radiotherapy only) for retinoblastoma

Study design (brief details):
Children who had received prior treatment for retinoblastoma and were in clinical remission were divided into two groups according to the treatment received. At approximately 7 years after treatment a series of tests was performed to determine whether treatment modality had an impact on levels of growth hormone, height and endocrine function

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not explicitly stated, although appears to be according to the actual treatment received as per hospital protocol

Sample size calculations:
Not reported

Statistical analyses:
Mean and SD of outcomes were calculated for each treatment group. No statistical comparisons between treatment groups were performed

Analysis by eyes or participants:
Participants

Inclusion criteria:
Participants were eligible for inclusion if they had been treated for retinoblastoma and if consent was obtained from a parent of the participant

Retinoblastoma classification system used:
Not reported

Note: The study used biological tests to investigate the impact of treatment modality on growth hormones and endocrine function in a subset of included patients. However, as this review is only concerned with clinical outcomes, data on growth and endocrine levels will not be reported

Interventions
Treatment 1:
No radiotherapy or retinal radiotherapy only

Dose, number of treatments, etc.
Retinal radiotherapy was delivered at a mean of dose 55 Gy (SD 16.9)

continued

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
The mean age at diagnosis was 24 months (SD 20 months) and the age at study was 125 months (SD 33 months)

Adjunctive treatments:
Chemotherapy with vicristine and cyclophosphamide weekly for 1 year

Treatment 2:
Cranial radiotherapy with or without orbital radiotherapy

Dose, number of treatments, etc.:
Cranial radiotherapy was delivered at 20–40 Gy (mean 29.3; SD 5.5) and orbital radiotherapy was delivered at 32–73 Gy (mean 45.42; SD 11.52)

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
The mean age at diagnosis was 23 months (SD 14 months) and the age at study was 128 months (SD 54 months)

Adjunctive treatments:
Chemotherapy with vincristine and cyclophosphamide weekly for 1 year

Participants
Number of participants allocated:
Total (*n*): 28
Treatment 1 (*n*): 10
Treatment 2 (*n*): 18

Number of eyes:
Total (*n*): not reported

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): none

Age of participants: Age of participants at start of study (age at diagnosis):
Total: mean 123 months (range 20–214 months); age at diagnosis mean 24 months (range 1–56 months)
Treatment 1: 125 months (SD 33 months); (age at diagnosis 24 months (SD 20 months)
Treatment 2: 128 months (SD 54 months); (age at diagnosis 23 months (SD 14 months)

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 10 patients received treatment for bilateral disease

Baseline tumour characteristics: Retinoblastoma classification:
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Other relevant baseline/tumour characteristics (insert details):
Age of participants at diagnosis of retinoblastoma:
Total (*n*): 24 months (range 1 month–56 months)
Treatment 1 (*n*): 24 months (SD 20 months)
Treatment 2 (*n*): 23 months (SD 14 months)

Results
Outcome 1
Description:
Height of participants normalised by expressing SDS according to the mean age and gender of participants reported as mean height score and SD

Treatment 1: 0.02 (1.2)
Treatment 2: –0.9 (1.3)

The authors report a statistically significant difference between treatment groups ($p < 0.05$)

Publication details
Authors (year):
Roarty *et al*. (1988)[115]

Country: USA

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To evaluate the incidence of SPTs in patients with bilateral retinoblastoma to determine the effect of radiation therapy

Study design (brief details):
The records of patients who had had an eye enucleated from 1922 to 1973 were reviewed. SPTs were classified as inside or outside the field of irradiation. Information on age at enucleation, gender, type of therapy, follow-up, latency time to the development of the SPT, type and location of SPT was obtained. The criteria used by Abramson *et al*. (1984)[138] were used to determine tumour location with respect to field of irradiation

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not stated

Sample size calculations:
Not stated

Statistical analyses:
The incidence of SPTs was calculated using life-table analysis. Mantel–Haenszel χ^2 analyses were used to compare life tables

Analysis by eyes or participants:
Participants

Inclusion criteria:
Patients with bilateral retinoblastoma who had an eye enucleated between 1922 and 1973 where the pathological specimen had been sent to the ROP at the Armed Forces Institute of Pathology were eligible for inclusion. Cases of SPTs were not included in the analysis if the samples were sent to the ROP without the enucleated eye having previously been studied

Retinoblastoma classification system used:
None

Interventions
Treatment 1:
Radiotherapy

Dose, number of treatments, etc.:
No details given

Period of treatment:
Not stated

Length of follow-up (mean, SD, range, etc.):
Median 7.2 years (range 0–49.1 years) (for both treatment groups combined)

Adjunctive treatments:
Not reported

Treatment 2:
No radiotherapy

Dose, number of treatments, etc.:
No details given

Period of treatment:
Not stated

Length of follow-up (mean, SD, range, etc.):
Median 7.2 years (range 0–49.1 years) (for both treatment groups combined)

Adjunctive treatments:
Not reported

continued

Participants
Number of participants allocated:
Total (*n*): 215
Treatment 1 (*n*): 137
Treatment 2 (*n*): 78

Number of eyes:
Total (*n*): 430
Treatment 1 (*n*): 274
Treatment 2 (*n*): 156

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported

Age of participants:
Total (*n*): not reported

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral):
Total (*n*): 215 bilateral
Treatment 1 (*n*): 137 bilateral
Treatment 2 (*n*): 78 bilateral

Baseline tumour characteristics: Retinoblastoma classification:
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Development of an SPT inside and outside the irradiation field. (Inside the field of irradiation was defined as origination in the lids, orbits, periocular sinuses, temporal bones or skin overlying the temporal bone; outside the field of irradiation was defined as tumours at distant sites and originating in the brain)

Treatment 1: 20/137 (13 inside field of irradiation, 7 outside)
Treatment 2: 4/78

Note: Two patients had two SPTs. Two of the tumours in treatment group 2 were pineoblastoma

Outcome 2
Description:
The 10-, 20- and 30-year incidence rate of SPTs (standard error) at all sites

Treatment 1: 8.3% (3.1); 23.5% (5.3); 35.1% (8.0)
Treatment 2: 1.6%(1.6); 5.8% (4.4); 5.8% (4.4)

The 30-year cumulative incidence of SPTs was significantly higher in patients who had received radiation ($p = 0.063$)

Publication details
Authors (year):
Scott *et al*. (1999)[121]

Country: USA

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To investigate eye conservation, local control and complications following treatment of retinoblastoma with two different types of EBRT

continued

Study design (brief details):
The records of all patients who received EBRT for retinoblastoma at two clinics from 1989 to 1996 were reviewed. The technique used was exclusively relative lens-sparing (RLS) at one clinic and exclusively modified lateral beam (MLB) at the second clinic

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Treatment was allocated according to the protocol used by the clinic

Sample size calculations:
Not reported

Statistical analyses:
Kaplan–Meier plots were used to summarise time-to-treatment failure and log-rank tests were used to compare the groups. Fisher's exact test was used to compare midfacial hypoplasia between groups
For tumour characteristics: Fisher's exact test, Student's *t*-test, Kendall's rank, exact-permutation χ^2 test and the Mann–Whitney test were used

Analysis by eyes or participants:
Eyes

Inclusion criteria:
Not reported

Retinoblastoma classification system used:
RE

Interventions
Treatment 1:
EBRT using the RLS technique to the 95% isodose line

Dose, number of treatments, etc.:
Mean radiation dose delivered was 43.5 Gy (SD 3.9) at 1.8 Gy per fraction (median dose 45 Gy; range 36–49 Gy)

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Mean 40.3 months (SD 20.8); median 39 months (range 5–74 months)

Adjunctive treatments:
Not reported

Salvage therapy:
Cryotherapy (2 eyes) or photocoagulation (1 eye)

Treatment 2:
EBRT using the MLB technique to the 95% isodose line

Dose, number of treatments, etc.:
Mean radiation dose delivered was 47.5 Gy (SD 2.6) at 1.8 Gy per fraction (median dose 48 Gy; range 44–54 Gy)

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Mean 36 months (SD 18.3). Median 36 months (range 7–72 months)

Adjunctive treatments:
Not stated

Salvage therapy:
Cryotherapy (5 eyes), photocoagulation (9 eyes) or chemotherapy (1 eye)

Participants
Number of participants allocated:
Total (*n*): 42
Treatment 1 (*n*): 18
Treatment 2 (*n*): 24

Number of eyes:
Total (*n*): 58
Treatment 1 (*n*): 26
Treatment 2 (*n*): 32

continued

Number of tumours:
Total (*n*) per eye: mean 3.1 (SD 2.3), median 2 (range 1–14)
Treatment 1 (*n*): 2.5 (1.7), 2 (1–7)
Treatment 2 (*n*): 3.7 (2.6), 3 (1–14)

Dropouts:
Total (*n*): not reported

Age of participants:
Total: mean 1 (SD 1.1), median 0.6 (range 0.02–5)
Treatment 1: 1.2 (1.5), 0.5 (0.02–5)
Treatment 2: 0.9 (0.7), 0.8 (0.03–2.1)

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 5 had unilateral retinoblastoma, 26 had unilateral EBRT
Treatment 1 (*n*): 2 had unilateral retinoblastoma, 10 had unilateral EBRT
Treatment 2 (*n*): 3 had unilateral retinoblastoma, 16 had unilateral EBRT

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): group I = 7, group II = 7, group III = 8, group IV = 12, group V = 24
Treatment 1 (*n*): group I = 3, group II = 2, group III = 5, group IV = 5, group V = 11
Treatment 2 (*n*): group I = 4, group II = 5, group III = 3, group IV = 7, group V = 13

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): 17
Treatment 1 (*n*): 10
Treatment 2 (*n*): 7

Baseline tumour characteristics: Retinal detachment:
Total (*n*): 23
Treatment 1 (*n*): 13
Treatment 2 (*n*): 10

Other relevant baseline/tumour characteristics: Number with retinal detachment involving the macular (not involving the macular)
Total (*n*): 14 (8) (data missing for one eye)
Treatment 1 (*n*): 8 (4) (data missing for one eye)
Treatment 2 (*n*): 6 (4) (data missing for one eye)

Other relevant baseline/tumour characteristics: Number with macular involvement; optic nerve involvement
Total (*n*): 37; 0
Treatment 1 (*n*): 15; 0
Treatment 2 (*n*): 22; 0

Result
Outcome 1
Description:
Eye conservation rates (the proportion of eyes without enucleation for each EBRT technique) for all RE classifications at 24-month follow-up

Treatment 1: 88.5%
Treatment 2: 89.1%

No statistically significant difference between treatment groups ($p = 0.4$)

Outcome 2
Description:
Rate of eye conservation (SD) in eyes with RE stages IV and V at 36-month follow-up

Treatment 1: 88% (8%)
Treatment 2: 83% (9%)

(*p*-value not given)

Outcome 3
Description:
Rate of tumour control without the need for salvage therapy for all RE stages at 24-month follow-up

Treatment 1: 84.6%
Treatment 2: 53.3%

Salvage therapy was performed significantly less frequently in patients treated with RLS compared with MLB ($p = 0.02$)

continued

Outcome 4
Description:
Rate of tumour control (SD) without the need for salvage therapy for eyes with RE stage IV and V at 36 months

Treatment 1: 81% (10%)
Treatment 2: 51% (12%)

No statistically significant difference between treatment groups ($p = 0.09$)

Outcome 5
Description:
Proportion of patients without cataract at 36-month follow-up

Treatment 1: 83.1%
Treatment 2: 63%

No statistically significant difference between treatment groups ($p = 0.4$)

Outcome 6
Description:
Proportion of patients with midfacial hypoplasia at 18-months follow-up

Treatment 1: 38.5%
Treatment 2: 29.4%

No statistically significant difference between treatment groups ($p = 0.7$)

Outcome 7
Description:
Other adverse events (number of patients) associated with treatment

Treatment 1: none reported
Treatment 2: radiation retinopathy (1), bilateral ptosis (2), restrictive strabismus (1)

MLB, modified lateral beam; RLS, relative lens sparing.

Publication details
Authors (year):
Shields *et al*. (1997)[133]

Country: USA

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To investigate chemoreduction and adjuvant treatment for retinoblastoma and its effect on retinal tumour control, and the control of vitreous and subretinal seeding

Study design (brief details):
Newly presenting patients with intraocular retinoblastoma at the Wills Eye Hospital who were treated from 1994 to 1996 with initial chemoreduction were identified. After commencement of chemoreduction the patient was examined under anaesthesia until complete control of the disease had been achieved, followed by examinations every 2–4 months as needed. Treatment outcome was compared for patients receiving less than 6 months and 6 months of chemotherapy, with or without adjuvant treatment

Retrospective/prospective
Prospective

How patients were allocated to their treatment group:
Chemotherapy: the initial treatment protocol, used in a pilot study, was for two cycles of chemotherapy, which was later changed to a six-cycle protocol with the aim of achieving better long-term tumour control
Adjuvant therapy: a decision regarding adjuvant treatment was made when maximum tumour regression was achieved. The general policy was to apply adjuvant treatment to all retinal tumours after chemotherapy. Adjuvant therapy was only applied to vitreous and subretinal seeds if they were incompletely regressed. The type of adjuvant treatment used was individually tailored according to tumour or seed size, location and status of the other eye. For tumour or seed base 3 mm or less the

continued

treatment options included thermotherapy, chemothermotherapy or laser photocoagulation if the tumour was posterior to the equator of the globe and cryotherapy if the mass was anterior; 3–12 mm thermotherapy or chemothermotherapy was applied preferentially with plaque therapy used if the tumour was anteriorly situated; 12 mm or greater plaque therapy was applied preferentially with thermotherapy or chemothermotherapy reserved for tumours near the optic disc and fovea. If vitreous or subretinal seeds were active or incompletely regressed plaque therapy was applied to focal seeds and EBRT or enucleation was recommended for diffuse seeds

Sample size calculations:
Not performed

Statistical analyses:
Fisher's exact test was used to compare outcome for the different treatment groups

Analysis by eyes or participants:
Tumours and eyes

Inclusion criteria:
New patients with intraocular retinoblastoma treated with initial chemoreduction with at least 1 year of follow-up examination, who according to published indications would normally require enucleation or EBRT for disease cure, were eligible
Patients were excluded if their tumour could be controlled successfully with conservative methods alone (cryotherapy, laser photocoagulation, thermotherapy, chemothermotherapy, plaque radiation therapy). Other exclusion criteria were biomicroscopic evidence of iris neovascularisation; neovascular glaucoma; tumour invasion into the anterior chamber, iris, optic nerve, choroids or extraocular tissues; evidence of systemic metastasis, prior chemotherapy, prior treatment for retinoblastoma; or inadequate functioning of the kidney, liver or ear

Retinoblastoma classification system used:
RE

Interventions
Treatment 1:
Chemotherapy of fewer than six cycles without adjuvant therapy

Dose, number of treatments, etc.:
Vincristine 1.5 mg m^{-2} (0.05 mg kg^{-1} for children 36 months or younger, maximum dose 2 mg); etoposide 150 mg m^{-2} (5 mg kg^{-1} for children 36 months or younger); carboplatin 560 mg m^{-2} (18.6 mg kg^{-1} for children 36 months or younger) Day 0, vincristine, etoposide and carboplatin; day 1, etoposide only; days 7, 14, 21, vincristine only (schedule A)

Period of treatment:
Fewer than six cycles of one cycle per month (exact length not specified)

Length of follow-up (mean, SD, range, etc.):
Mean 19 months for treatment (for six cycles of chemotherapy with or without adjuvant treatment)

Adjunctive treatments:
None

Treatment 2:
Chemotherapy of fewer than six cycles with adjuvant therapy

Dose, number of treatments, etc.:
Schedule A, as described above

Period of treatment:
Fewer than six cycles of chemotherapy (exact length not specified)

Length of follow-up (mean, SD, range, etc.):
Mean 19 months for treatment for six cycles of chemotherapy (with or without adjuvant treatment)

Adjunctive treatments
Cryotherapy, laser photocoagulation, thermotherapy, chemothermotherapy, plaque therapy or EBRT

Treatment 3
Six cycles of chemotherapy without adjuvant therapy

Dose, number of treatments. etc.:
Vincristine 1.5 mg m^{-2} (0.05 mg kg^{-1} for children 36 months or younger, maximum dose 2 mg); etoposide 150 mg m^{-2} (5 mg kg^{-1} for children 36 months or younger); carboplatin 560 mg m^{-2} (18.6 mg kg^{-1} for children 36 months or younger) Day 0, vincristine, etoposide and carboplatin; day 1, etoposide only (schedule B)

Period of treatment:
Six cycles of one cycle per month

continued

Length of follow-up (mean, SD, range, etc.):
Mean 16 months for treatment for six cycles of chemotherapy (with or without adjuvant treatment)

Adjunctive treatments:
None

Treatment 4:
Six cycles of chemotherapy with adjuvant therapy

Dose, number of treatments, etc.:
Schedule B, as described above

Period of treatment:
Six cycles of one cycle per month

Length of follow-up (mean, SD, range, etc.):
Mean 16 months for treatment for six cycles of chemotherapy (with or without adjuvant treatment)

Adjunctive treatments:
Cryotherapy, laser photocoagulation, thermotherapy, chemothermotherapy, plaque therapy or EBRT

Note: Overall mean length of follow-up 17 months (range 13–27 months)

Participants
Number of participants allocated:
Total (*n*): 32
Treatments 1 and 2 (*n*): 18
Treatments 3 and 4 (*n*): 14

Number of eyes:
Total (*n*): 52
Treatments 1 and 2 (*n*): 25
Treatments 3 and 4 (*n*): 27

Number of tumours:
Total (*n*): 130
Treatment 1 (*n*): 1
Treatment 2 (*n*): 52
Treatment 3 (*n*): 8
Treatment 4 (*n*): 69

Dropouts:
Total (*n*): 1 (1/33 patients initially enrolled had follow-up at another centre and was excluded)

Age of participants (at presentation):
Total: mean 13 months (median 12 months; range 1–46 months)

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): bilateral 19 patients, unilateral 13 patients, familial 5, sporadic 27

Baseline tumour characteristics: retinoblastoma classification (RE):
Total (*n*): group I = 1, group II = 5, group III = 9 eyes, group IV = 1, group V = 36

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): 24 eyes
Treatment 1 (*n*): 0
Treatment 2 (*n*): 13
Treatment 3 (*n*): 4
Treatment 4 (*n*): 7

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): 28
Treatment 1 (*n*): 6
Treatment 2 (*n*): 8
Treatment 3 (*n*): 6
Treatment 4 (*n*): 8

Other relevant baseline/tumour characteristics: Mean pretreatment retinal tumour size and mean tumour thickness:
Total (*n*): mean pretreatment retinal tumour size: 9 mm base (median 7 mm, range 0.5–24 mm); mean tumour thickness: 6 mm (median 5 mm, range 0.5–17 mm)

Treatments 1 and 2: mean pretreatment retinal tumour size: 10 mm base, 7 mm thickness
Treatments 3 and 4: mean pretreatment retinal tumour size: 8 mm base, 5 mm thickness

continued

Result
Outcome 1
Description:
Mean post-treatment retinal tumour size

Treatment 1 and 2: 6 mm base; 2 mm thickness
Treatment 3 and 4: 6 mm base; 2 mm thickness

Outcome 2
Description: Retinal tumour recurrence

Treatment 1: 0% (0/1)
Treatment 2: 2% (1/52)
Treatment 3: 12% (1/8)
Treatment 4: 1% (1/69)

No statistically significant differences between treatment groups ($p = 0.26$)

Outcome 3
Description:
Vitreous seed recurrence

Treatment 1: 12% (1/8)
Treatment 2: 24% (4/17)
Treatment 3: 18% (3/17)
Treatment 4: 0% (0/10)

No statistically significant difference when the treatments were compared, regardless of whether vitreous seeds were present or absent before treatment, or when the treatments were compared for the 28 eyes with no vitreous seeds pretreatment ($p = 0.48$ and $p = 0.54$, respectively)

Statistically significant difference when the four treatments were compared for the 24 eyes with vitreous seeding pretreatment ($p = 0.04$)

Outcome 4
Description:
Subretinal seed recurrence

Treatment 1: 58% (7/12)
Treatment 2: 31% (4/13)
Treatment 3: 32% (6/19)
Treatment 4: 0% (0/8)

No statistically significant difference when the treatments were compared regardless of whether subretinal seeds were present or absent before treatment, or when the treatments were compared for the 24 eyes with no subretinal seeds pretreatment ($p = 0.06$ and $p = 0.55$, respectively)

Statistically significant difference when the treatments were compared for the 28 eyes with subretinal seeding pretreatment ($p = 0.003$)

Outcome 5
Description:
Final ocular management following recurrent retinal tumour, vitreous seeds or subretinal seeds according to initial RE classification

Group I (1 eye): local treatment $n = 1$
Group II (5 eyes): EBRT $n = 2$, local treatment $n = 3$
Group III (9 eyes): local treatment $n = 9$
Group IV (1 eye): EBRT $n = 1$
Group V (36 eyes) enucleation $n = 8$, EBRT $n = 19$, local treatment $n = 8$, no additional treatment $n = 1$

Note: Of the five eyes that received chemotherapy alone (six cycles) with no adjuvant therapy, despite clinically complete regression at 2-month follow-up, four eyes had retinal tumour or seed recurrence at a mean of 8 months after the initiation of chemotherapy, which were treated with EBRT in two eyes, cryotherapy in one eye and enucleation in one eye

Publication details
Authors (year):
Shields *et al*. (2001)[131]

Country: USA

Type of publication (full paper, abstract):
Full paper

Note: The data have also been presented in abstract format.[157]

Study design
Authors' objective:
To evaluate whether neoadjuvant intravenous chemotherapy (chemoreduction) for retinoblastoma reduces the risk for associated intracranial neuroblastic tumour (trilateral retinoblastoma)

Study design (brief details):
The medical records of all patients with newly diagnosed retinoblastoma who were managed from 1995 to 1999 at the Wills Eye Hospital, Philadelphia, were reviewed with the above objective in mind. Patients were divided into those who had received chemoreduction therapy at any point during their treatment, and those who had not received chemoreduction therapy at any time point during treatment for retinoblastoma. All patients underwent annual or biannual routine MRI or CT of the CNS until aged 4 or 5 years to ascertain the development of pineal tumour or other intracranial neuroblastic tumours

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Based on hospital protocol: children with intraocular retinoblastoma who otherwise would require treatment with EBRT or enucleation were generally allocated to receive chemoreduction

Sample size calculations:
The power of the study was estimated based on the assumption that the data had a binomial distribution and a statistical significance level of 0.05. Based on a sample size of 99 children at risk of developing an intracranial tumour, the power was calculated as 1.0

Statistical analyses:
The expected number of patients developing trilateral retinoblastoma was based on a published meta-analysis.[18] Statistical significance of observed cases of trilateral retinoblastoma was calculated using binomial distribution formula using software that simultaneously examined the number of observed cases of trilateral retinoblastoma, the number of patients seen to arrive at the observed cases and the expected probability of developing trilateral retinoblastoma, and the assumption that the equation is true

Analysis by eyes or participants:
Participants

Inclusion criteria:
Children with newly diagnosed retinoblastoma treated at the Wills Eye Hospital from January 1995 to July 1999 were eligible for inclusion

Retinoblastoma classification system used:
The authors report that the RE system was used to classify patients; however, the data are not presented in the report

Interventions
Treatment 1:
Chemoreduction therapy at any point during treatment. The chemoreduction protocol of the study clinic included vincristine sulphate, etoposide phosphate and carboplatin

Dose, number of treatments, etc.:
Vincristine sulphate was administered at a dose of 1.5 mg m^{-2} (0.05 mg kg^{-1} for children aged ≤ 36 months, maximum dose <2 mg); etoposide phosphate at a dose of 150 mg m^{-2} (5 mg kg^{-1} for children aged <36 months); and carboplatin at a dose of 560 mg m^{-2} (18.6 mg kg^{-1} for children aged ≤ 36 months). Each therapy was given on day 0, and etoposide was again given on day 1 of the 28-day cycle

Period of treatment:
Mean number of 28-day cycles given was 5 (range 2–13 cycles)

Length of follow-up (mean, SD, range, etc.):
Mean 34 months (median 6; range 0–67 months)

Adjunctive treatments:
Patients received focal adjuvant therapy

continued

Treatment 2:
No chemoreduction therapy was given at any point during therapy. The therapy given to this group of patients was not reported. The authors report that patients will have received EBRT, brachytherapy, thermotherapy, laser photocoagulation, or cryotherapy

Dose, number of treatments, etc.:
Not reported

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Mean 30 months (median 31, range 5–58 months). The authors report that the study period was 54 months

Adjunctive treatments:
Not reported

Participants
Number of participants allocated:
Total (*n*): 214
Treatment 1 (*n*): 142
Treatment 2 (*n*): 72

Number of eyes:
Total (*n*): not reported

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): not reported

Age of participants:
Total: not reported
Treatment 1: mean age at diagnosis: 14 months (median 8, range 1–87 months); mean age at date last seen: 47 months (median 44, range 8–134 months)
Treatment 2: mean age at diagnosis: 24 months (median 22; range 1–110 months); mean age at date last seen 54 months (median 52, range 9–120 months)

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 102 unilateral and 112 bilateral; 176 sporadic and 38 familial (33 bilateral and 5 unilateral)
Treatment 1 (*n*): 47 unilateral and 95 bilateral; 111 sporadic and 31 familial (27 bilateral and 4 unilateral)
Treatment 2 (*n*): 55 unilateral and 17 bilateral; 65 sporadic and 7 familial (6 bilateral and 1 unilateral)

Baseline tumour characteristics: Retinoblastoma classification (RE or equivalent):
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Other relevant baseline/ tumour characteristics: Number of patients at risk of developing intracranial neuroblastic tumour (defined as the number of patients with bilateral or familial retinoblastoma)
Total (*n*): 117
Treatment 1 (*n*): 99
Treatment 2 (*n*): 18

Result
Outcome 1
Description
Comparison of the prevalence of associated intracranial neuroblastic tumour (trilateral retinoblastoma) in all patients with retinoblastoma [expected number of cases (E) (%) and observed number of cases (O) (%)] (all patients)

Treatment 1: E = 4 (3%); O = 0 (0%)
Treatment 2: E = 2 (3%); O = 1 (1%)

The patient in the non-chemoreduction treatment group went on to develop a pineoblastoma diagnosed 26 months after initial diagnosis of retinoblastoma, and the patient died 19 months later

continued

Outcome 2
Description:
Comparison of the prevalence of associated intracranial neuroblastic tumour in at-risk patients [number of patients at-risk; expected number of cases (E) (%) and observed number of cases (O) (%)]

Treatment 1: 99 patients at risk; E = 5–15 (5 to 15%); O = 0 (0%)
Treatment 2: 18 patients at risk; E = 1–3 (5 to 15%); O = 1 (6%)

There was a statistically significant reduction in the expected number of patients with intracranial neuroblastic tumour who were given chemoreduction ($p < 0.01$)

In the non-chemoreduction group the observed number of patients who developed an intracranial neuroblastic tumour was consistent with the expected number of patients

Outcome 3
Description:
Comparison of the prevalence of associated intracranial neuroblastic tumour in patients with unilateral sporadic retinoblastoma [number of patients at risk; expected number of cases (E) (%) and observed number of cases [O] (%)]

Treatment 1: 43 patients with unilateral sporadic disease; E < 1 (0.05%); O = 0
Treatment 2: 54 patients with unilateral sporadic disease; E < 1 (0.05%); O = 0

There was no statistically significant difference in the observed and expected prevalence of intracranial neuroblastic tumour in patients with unilateral sporadic retinoblastoma treated with chemoreduction

Publication details
Authors (year):
Srivastava *et al*. (1984)[118]

Country: India

Type of publication (full paper, abstract):
Full paper

Study design
Authors' objective:
To determine the efficacy of different treatment modalities used in patients with retinoblastoma

Study design (brief details):
64 children with retinoblastoma registered at King George's Medical College, Lucknow, who were treated for retinoblastoma with ^{60}Co teletherapy alone, surgical enucleation alone, or surgical enucleation and ^{60}Co teletherapy between 1970 and 1979 were reviewed to determine survival associated with the different modes of treatment

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Patients were allocated to treatment group according to stage of disease: surgery alone was undertaken only for stages I and II, and stage III patients were treated with surgery followed by ^{60}Co teletherapy. Patients with stage IV retinoblastoma, where the tumour was inoperable, were treated by ^{60}Co teletherapy alone

Sample size calculations:
Not performed

Statistical analyses:
Number and percentage of patients with outcome of interest in each treatment modality were reported. No statistical comparisons of treatment groups were performed

Analysis by eyes or participants:
Participants

Inclusion criteria:
Not reported

Retinoblastoma classification system used:
Stages as proposed by Miller: stage I quiescent stage, stage II glaucomatous stage, stage III extraocular extension, stage IV metastasis

continued

Interventions
Treatment 1:
Radiotherapy alone using ^{60}Co teletherapy

Dose, number of treatments, etc.:
Doses varied from 35–40 Gy

Period of treatment:
3–4 weeks

Length of follow-up (mean, SD, range, etc.):
The exact length of follow-up is not given in the report. One patient was followed up for <1 year, 7 patients for 1–3 years, 6 patients for 3–5 years and 4 patients for >5 years

Adjunctive treatments:
Not reported

Treatment 2:
Surgery (enucleation)

Dose, number of treatments, etc.:
Not applicable

Period of treatment:
Not applicable

Length of follow-up (mean, SD, range, etc.):
The exact length of follow-up is not given in the report. One patient was followed up for 3–5 years and 2 patients for >5 years

Adjunctive treatments:
Not reported

Treatment 3:
Surgery (enucleation) and radiotherapy using ^{60}Co teletherapy

Dose, number of treatments, etc.:
Doses varied from 35–40 Gy

Period of treatment:
3–4 weeks

Length of follow-up (mean, SD, range, etc.):
The exact length of follow-up is not given in the report. One patient was followed up for <1 year, 3 patients for 1–3 years, 4 patients for 3–5 years and 6 patients for >5 years

Adjunctive treatments:
Not reported

Participants
Number of participants allocated:
Total (*n*): 64

Number of eyes:
Total (*n*): 69

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): 29 (54/64 patients were followed up, of whom 19 had incomplete treatment or refused treatment)

Age of participants:
Total: not reported

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic):
Total (*n*): 59 unilateral, 5 bilateral

Baseline tumour characteristics: Retinoblastoma classification (Miller staging)
Total (*n*): 3 stage II, 14 stage III, 18 stage IV
Treatment 1 (*n*): 18, all stage IV
Treatment 2 (*n*): 3, all stage II
Treatment 3 (*n*): 14, all stage III

continued

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Result
Outcome 1
Description:
Survival at <1 year, 1–3 years, 3–5 years and >5 years (number of patients followed up at respective time-point)

Treatment 1: 1 (1), 4 (7), 3 (6), 0 (4) (all cases with stage IV tumour)
Treatment 2: 0 (0), 0 (0), 0 (1), 0 (2) (all cases with stage II tumour)
Treatment 3: 1 (1), 2 (3), 4 (4), 3 (6) (all cases with stage III tumour)

Publication details
Authors (year):
Sussman *et al*. (2003)[111]

Country: USA

Type of publication (full paper, abstract):
Full paper

Related abstract publications:
Miracle *et al*. (2003)[158] and Sussman *et al*. (2002)[159]

Study design
Authors' objective:
To determine the time-course and extent of tumour reduction associated with systemic chemoreduction and EBRT used for the treatment of advanced intraocular retinoblastoma

Study design (brief details):
The medical, photographic and echographic records of all children with RE stage IV and V retinoblastoma who completed primary eye-conserving treatment with systemic chemotherapy or EBRT at a single centre from 1991 to 2001 were reviewed to determine the impact of the different treatment modalities on tumour volume, tumour reduction, regression patterns, treatment-related complications, metastases, eye conservation and survival

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Patients were allocated to treatment group according to RE stage. At the clinic that conducted the research stages I, II and III were treated initially with focal therapy, whereas stages IV and V were treated initially with chemoreduction or EBRT

Sample size calculations:
Not performed

Statistical analyses:
Fisher's exact test or the χ^2 test was used to assess statistical significant differences between treatment groups for categorical variables, or the two-sample *t*-test for continuous variables

Analysis by eyes or participants:
Eyes

Inclusion criteria:
Patients had to have complete photographic and/or echographic documentation to enable accurate measurement of tumour size
Patients with RE stages IV and V
Patients were excluded if they had initially been treated at a different institute to the study institute, or if they required primary enucleation

Retinoblastoma classification system used:
RE

Interventions
Treatment 1:
Chemotherapy using carboplatin, vincristine sulphate and etoposide phosphate with or without cyclosporine

continued

Dose, number of treatments, etc.:
Carboplatin: 20 mg kg^{-1} for patients <12 months and 550–600 mg m^{-2} BSA for patients > 12 months
Vincristine: 0.05 mg kg^{-1} <12 months and 1.5–2 mg m^{-2} BSA >12 months
Etoposide: 5 mg kg^{-1} <12 months and 150 mg m^{-2} BSA >12 months
Cyclosporine: 5 mg kg^{-1} per hour bolus for 2 hours before chemotherapy, then 1.5 mg kg^{-1} per hour infusion for the next 30 hours if patient weighed <12 kg, or 4 mg kg^{-1} per hour and 1.25 mg kg^{-1} per hour if patient weighed between 12 and 30 kg, or 3 mg kg^{-1} per hour and 1 mg kg^{-1} per hour if patient weighed >30 kg

Period of treatment:
Chemotherapy was given every 3 weeks with a target of nine cycles (mean received seven)

Length of follow-up (mean, SD, range, etc.):
Mean 35 months (range 6–72 months). Miracle *et al*. (2003)[158] and Sussman *et al*. (2002)[159] report a median follow-up of 61 months

Adjunctive treatments:
All patients received transpupillary diode laser therapy, and some (50%) also received cryotherapy at the time of examination under anaesthesia immediately before the cycles of chemotherapy

Treatment 2:
EBRT delivered using the RLS technique that included treatment to the 95% isodose line

Dose, number of treatments, etc.:
43.2–45 Gy delivered in a single daily fraction of 1.8 Gy

Period of treatment:
Approximately 3 weeks

Length of follow-up (mean, SD, range, etc.):
Mean 35 months (range 6–72 months). Miracle *et al*. (2003)[158] and Sussman *et al*. (2002)[159] report a median follow-up of 61 months

Adjunctive treatments:
None (2), transpupillary diode laser therapy (1), cryotherapy (2), or diode laser and cryotherapy (3)

Participants
Number of participants allocated:
Total (*n*): 26
Treatment 1 (*n*): 18 (9 treated with cyclosporine)
Treatment 2 (*n*): 8

Number of eyes:
Total (*n*): 26
Treatment 1 (*n*): not reported
Treatment 2 (*n*): not reported
Miracle *et al*. (2003)[158] and Sussman *et al*. (2002)[159] report data for 38 eyes

Number of tumours:
Total (*n*): 26 (if more than one tumour was present then only the largest at baseline was included in the analysis. It is unclear whether for patients with bilateral disease only one eye was included)
Treatment 1 (*n*): 18
Treatment 2 (*n*): 8

Dropouts:
Total (*n*): not applicable (complete documentation was an inclusion criterion)
Treatment 1 (*n*): not applicable
Treatment 2 (*n*): not applicable

Age of participants:
Total: 11 months (SD 12)
Treatment 1: 9 months (SD 11)
Treatment 2: 17 months (SD 15)

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral; hereditary vs sporadic)
Total (*n*): 21 bilateral, 5 unilateral; 8 hereditary, 18 sporadic
Treatment 1 (*n*): 14 bilateral, 4 unilateral; 8 hereditary, 10 sporadic
Treatment 2 (*n*): 7 bilateral, 1 unilateral; 0 hereditary, 8 sporadic

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): group IV or V = 13, group Vb = 13 (vitreous seeding)
Treatment 1 (*n*): group IV or V = 10, and group Vb = 8
Treatment 2 (*n*): group IV or V = 3, and 5 group Vb = 5

continued

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): 13
Treatment 1 (*n*): 8
Treatment 2 (*n*): 5

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Result

Outcome 1

Description:
Tumour volume calculated using radius, basal area and height values determined by ultrasound, physical examination and a photographic review [mean percentage (SD) of baseline volume]

Treatment 1: 32 (26) reduction at 1 month; 19 (15) at 2 months; 16 (16) at 3 months; 8 (14) at 6 months; 9 (17) at 12 months
Treatment 2: 88 (32) reduction at 1 months; 42 (32) at 2 months; 25 (18) at 3 months; 23 (15) at 6 months; 6 (2) at 12 months

Differences between groups: at 1 month $p = 0.004$, at 2 months $p = 0.04$, at 3 months $p = 0.4$, at 6 months $p = 0.2$, and at 12 months $p = 0.76$

Outcome 2

Description:
Number of patients with local treatment-related complications

Treatment 1: vitreous haemorrhage (3); vasculopathy (1); optic neuropathy (1); cataract (0); optic disc swelling (1); retinopathy (0); midfacial hypoplasia (0)
Treatment 2: vitreous haemorrhage (1); vasculopathy (0); optic neuropathy (0); cataract (7); optic disc swelling (0); retinopathy (0); midfacial hypoplasia (2)

There were no statistically significant differences between treatment groups for any of the local treatment complications, with the exception of the number of patients with a cataract ($p < 0.001$), which was significantly higher in the EBRT group

Outcome 3

Description:
Number of patients with conserved globes following treatment (%)

Treatment 1: 18 (100%)
Treatment 2: 8 (100%)

Outcome 4

Description:
Percentage of patients who had survived at time of last follow-up

Treatment 1: 100%
Treatment 2: 100%

Outcome 5

Description:
Percentage of patients who were metastasis free at time of last follow-up

Treatment 1: 100%
Treatment 2: 100%

Data from related publications[158,159]

Description:
Tumour volume calculated using basal area and height values determined by ultrasound, physical examination and a photographic review (mean percentage of baseline volume)

Treatment 1: 82%[a]
Treatment 2: 65%[a]

[a] The results are presented after 2 cycles of chemotherapy, and for a comparable time-point postradiation therapy

No metastatic disease or mortality was noted[158]

Chemotherapy was associated with a statistically significant greater reduction in tumour volume after two cycles compared with a similar time-point after EBRT ($p < 0.05$). However, there was no statistically significant reduction in tumour volume between treatment modalities at 12 months post-treatment

continued

Publication details
Authors (year):
Wolff *et al*. (1981)[107]

Country: USA

Type of publication (full paper, abstract):
Conference proceeding

Study design
Authors' objective:
To evaluate the use of adjuvant chemotherapy to reduce mortality and identify patient and disease characteristics of prognostic importance

Study design (brief details):
Children with a histological diagnosis of unilateral intraocular retinoblastoma classified as RE group V who presented to the CCSG or POG from June 1977 were either randomly assigned or non-randomly allocated to receive adjuvant chemotherapy following surgical enucleation or a control with no-chemotherapy regimen

Retrospective/prospective:
Prospective

How patients were allocated to their treatment group:
54 of the evaluated patients were randomly allocated treatment groups and 34 of evaluated patients were not randomly allocated to treatment groups. It is not clear how non-randomised patients were assigned to treatment groups

Sample size calculations:
Sample size calculations were based on a 7% reduction in mortality with the addition of chemotherapy to enucleation with a statistical significance of $p = 0.05$ and 75% power between treatment groups. It was estimated that 110 patients in each of the chemotherapy and non-chemotherapy group would be required

Statistical analyses:
The authors appear to have used Kaplan–Meier survival curves to compare mortality between treatment groups, although they are not referred to as such. Similarly, tests of statistical significance were performed but information on the test used was not given in the report

Data on patients who relapsed, site of relapse and time to relapse were presented for each treatment group. No statistical comparisons were performed

Analysis by eyes or participants:
Participants

Inclusion criteria:
All children with a histological diagnosis of unilateral intraocular retinoblastoma (RE group V) were eligible for inclusion
At study onset patients with optic nerve involvement proximal to the cut end of the nerve were eligible for inclusion. The protocol was amended in March 1979 to exclude patients with tumour in the optic nerve distal to the lamina cribrosa, as the only two patients with this diagnosis had already relapsed in the CNS

Retinoblastoma classification system used:
RE

Note: The authors state that the study ceased patient enrolment 8 months earlier than projected owing to a slower than expected accrual of patients. In addition, the assumed 17% mortality of patients with unilateral intraocular retinoblastoma had not been confirmed by the study (it was lower in both treatment groups)

Interventions
Treatment 1:
Enucleation and adjuvant chemotherapy with cyclophosphamide and vincristine

Dose, number of treatments, etc.:
Cyclophosphamide given at a dose of 30 mg kg^{-1} and vincristine at a dose of 0.05 mg kg^{-1}

Period of treatment:
Regimen was given every 3 weeks for a total of 57 weeks

Length of follow-up (mean, SD, range, etc.):
For patients recruited from CCSG, median length of follow-up was 23 months (mean 23 months). For patients recruited from POG, median length of follow-up was 21 months (mean 22 months)

Adjunctive treatments:
No other adjuvant therapy reported

continued

Treatment 2:
Enucleation only

Dose, number of treatments, etc.:
Not applicable

Period of treatment:
Not applicable

Length of follow-up (mean, SD, range, etc.):
For patients recruited from CCSG, median length of follow-up was 22 months (mean 20 months). For patients recruited from POG, median length of follow-up was 16 months (mean 13 months)

Adjunctive treatments:
No other adjuvant therapy reported

Participants
Number of participants allocated:
Total (*n*): 88
Treatment 1 (*n*): 43 (27 patients were randomised and a further 16 patients were not randomly allocated)
Treatment 2 (*n*): 45 (27 patients were randomised and a further 18 patients were not randomly allocated)

Note: There were 93 patients originally allocated, but 5 were not included in the analysis as it later became apparent that they had bilateral disease. Only 88 met the inclusion criteria

Number of eyes:
Total (*n*): 88 (evaluated in the analysis)
Treatment 1 (*n*): 43
Treatment 2 (*n*): 45

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): 12 lost to follow-up; 4 withdrawn
Treatment 1 (*n*): 3 lost to follow-up, 4 were withdrawn, of whom 2 were reported to have experienced treatment-related side-effects
Treatment 2 (*n*): 9 lost to follow-up (8 were randomly allocated to treatment and 1 was non-randomly allocated)

Age of participants:
Total: not reported

Baseline tumour characteristics: Type of retinoblastoma (number bilateral vs unilateral):
Total (*n*): 88 unilateral
Treatment 1 (*n*): 43 unilateral
Treatment 2 (*n*): 45 unilateral

Baseline tumour characteristics: Retinoblastoma classification (RE):
Total (*n*): group V = 88
Treatment 1 (*n*): group V = 43
Treatment 2 (*n*): group V = 45

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Results
Outcome 1
Description:
Survival at 2 years (percentage of patients)

Treatment 1: 87.6%
Treatment 2: 95%

continued

No statistically significant difference in survival between those who received adjuvant chemotherapy and those that did not ($p = 0.368$)
The authors state that there was no decline in survival rates after 2 years (data not provided). They also state that there was no apparent difference in disease-free survival or survival due to age group or gender

Outcome 2
Description:
Number of patients who relapsed (site of relapse, months to relapse)
Treatment 1: 4 (2 patients were randomly allocated to treatment and 2 were non-randomly allocated) (CNS, 9 months; bone marrow, 6 months; orbit, optic foramen, CNS, 3 months[a]; optic chiasm, 12 months[a])
Treatment 2: 3 (all three patients were randomly allocated to treatment) (bone marrow, 4 months; CNS, 2 months; bone marrow, liver, spleen and orbit, 8 months)

[a] These patients were followed up but not randomised to treatment group 1

Outcome 3
Description:
Number of patients with reported treatment-related side-effects

Treatment 1: 2 (both patients experienced generalised non-fatal reactions to cyclophosphamide)
Treatment 2: 0

CCSG, Children's Cancer Study Group; POG, Pediatric Oncology Group

Publication details
Authors (year):
Wong *et al.*, (1997)[5]

Country: USA

Type of publication (full paper, abstract):
Full paper

Related publications:
Kleinerman *et al*. (1999)[160]; Kleinerman *et al*. (Radiation Epidemiology Branch, National Cancer Institute: personal communication, 2004); Abramson *et al*. (1998)[137]; Abramson *et al*. (1984)[138]

Study design
Authors' objective:
To examine long-term risk of new primary cancers in survivors of childhood retinoblastoma and quantify the role of radiotherapy in sarcoma development

Study design (brief details):
A cohort incidence study of new primary tumours in retinoblastoma patients including a comparison of radiotherapy treatment with no radiotherapy treatment and a nested case–control study of a radiation dose–response relationship for bone and soft-tissue sarcomas

Retrospective/prospective:
Retrospective

How patients were allocated to their treatment group:
Not reported

Sample size calculations:
Not reported

Statistical analyses:
Cohort analyses: observed and expected numbers of cancers were compared. Expected numbers were estimated by multiplying appropriate person years at risk by gender, age and calendar year-specific cancer rates from a population-based cancer registry. Exact Poisson probabilities were used to calculate significance and CIs. Excess risk was defined as observed minus expected number of cancers, divided by the number of person-years at risk. The Kaplan–Meier method was used to estimate the cumulative incidence of second cancers
Case–control analyses: radiation doses were estimated at the site of the sarcoma for each case, and for controls anatomical sites of sarcoma were randomly assigned according to the frequency distribution of sites of sarcoma in cases. Risk of sarcoma at each dose category relative to the lowest category (0–4.9 Gy), approximated by the OR was modelled as 1 plus the excess RR. The reported OR was the median from 201 repeats of randomised 'site-matched dose' assignments in controls adjusted for age at retinoblastoma diagnosis and length of follow-up. A bootstrap resampling method was used to estimate 95% CIs

continued

Analysis by eyes or participants:
Participants

Inclusion criteria:
Cohort: retinoblastoma patients identified from hospital records in Boston (1937–1984) and New York (1914–1984) who survived for 1 year or more after diagnosis, resided or died in the USA and were known to be alive in 1925 or later
Case–control: cases were patients from the cohort identified with sarcoma based on data available from the first follow-up interview (1987–1988). 100 controls were selected (randomly) on the basis of having bilateral retinoblastoma and being free of second cancer. Only patients whose radiation dosimetry quality scores for completeness of information were fair or better were included in the analysis. Patients with leg and trunk bone sarcomas were excluded from the analysis owing to each estimated bone dose to legs and trunk being less than 5 Gy

Retinoblastoma classification system used:
Not reported

Interventions
Treatment 1:
Cohort: radiotherapy

Dose, number of treatments, etc.:
Before 1960 the majority of patients received orthovoltage radiation. After then, nearly all patients received ^{60}Co teletherapy or betatron (22 MV) or other megavoltage (mostly 6 MV) machines. After 1980, 21 patients received electron beam therapy (extracted from Wong[5]). Average dose 48 Gy (range 15–115 Gy) in 15 fractions (extracted from Kleinerman *et al*.: personal communication, 2004)

Period of treatment:
Several weeks (extracted from Kleinerman *et al*., 2004)

Length of follow-up (mean, SD, range ,etc.):
Median length of follow-up was 20 years for total cohort (follow-up began 1 year after diagnosis and ended at date of loss to follow-up, date of death or December 1993). Kleinerman *et al*. (2004) provide data updated to 31 December 2000: mean length of follow-up 25.2 years for hereditary retinoblastoma patients, and 29.5 years for hereditary patients across treatment groups

Adjunctive treatments:
Not reported

Treatment 2:
Cohort: no radiotherapy

Dose, number of treatments, etc.:
Not reported

Period of treatment:
Not reported

Length of follow-up (mean, SD, range, etc.):
Median length of follow-up 20 years for total cohort (follow-up began 1 year after diagnosis and ended at date of loss to follow-up, date of death or December 1993). Kleinerman *et al*. (2004) provide data updated to 31 December 2000: mean length of follow-up 25.2 years for hereditary retinoblastoma patients and 29.5 years for non-hereditary patients across treatment groups

Adjunctive treatments:
Not reported

Case–control:
63 cases with bone sarcoma and 37 cases with soft-tissue sarcoma. Analysis was restricted to 83 patients (52 with bone sarcoma, 31 with soft-tissue sarcoma) whose radiation completeness of information ratings were fair or better

Radiation dose
Information on radiation treatment was obtained from radiotherapy records. Measurements and computer simulations estimated absorbed dose. The average of the minimum and maximum calculated doses was used where there was uncertainty regarding treatment field or precise location of subsequent tumours

Dose, number of treatments, etc.:
Treatment 1: 0–4.9 Gy; treatment 2: 5.0–9.9 Gy; treatment 3: 10.0–29.9 Gy; treatment 4: 30.0–59.9 Gy; treatment 5: ≥ 60.0 Gy

Period of treatment:
Not reported

continued

Length of follow-up (mean, SD, range, etc.):
Not reported

Adjunctive treatments:
Not reported

Participants
Number of participants allocated:
Total (*n*): cohort 1604
Treatment 1 (*n*): 962
Treatment 2 (*n*): 642

Total (*n*): Case–control study 100 cases (83 in analysis), 100 controls

Number of eyes:
Total (*n*): not reported

Number of tumours:
Total (*n*): not reported

Dropouts:
Total (*n*): cohort: 112 lost to follow-up
Treatment 1 (*n*): not reported
Treatment 2 (*n*): not reported
Total (*n*): case–control study: 33 cases excluded (17 due to dosimetry scores of less than fair quality and 16 leg or trunk bone sarcoma cases), 11 controls (no reasons reported)

Age of participants:
Total: cohort: hereditary median age at diagnosis 10 months, non-hereditary median age at diagnosis 23 months
Treatment 1: not reported
Treatment 2: not reported

Baseline tumour characteristics: Type of retinoblastoma (patients with bilateral tumours or unilateral tumour with a family history of retinoblastoma were classified as hereditary)
Total (*n*): cohort: 961 (60%) hereditary; 643 non-hereditary
Treatment 1 (*n*): hereditary 848, non-hereditary 114
Treatment 2 (*n*): hereditary 113, non-hereditary 529

Baseline tumour characteristics: Retinoblastoma classification (RE or equivalent):
Total (*n*): not reported

Baseline tumour characteristics: Vitreous seeding:
Total (*n*): not reported

Baseline tumour characteristics: Subretinal seeding:
Total (*n*): not reported

Result
Outcome 1: cohort
Description:
Observed (O) number of new cancers. (Data were obtained from medical records and patient interviews. Unconfirmed cancers, benign tumours and all primary cancers of the skin other than malignant melanoma were excluded. Approximately 60% of cancers were classified histologically based on pathology reports.) Expected (E) number of new cancers, ratio of observed to expected cancers (O/E) and excess risk (see statistical analyses above)

Treatment 1: hereditary: O = 180; E = 4.91; O/E = 36.7 (95% CI 31.6 to 42.5); excess risk 10.9; non-hereditary: O = 3; E = 1.11; O/E = 2.7 (95% CI 0.6 to 7.9); excess risk 1.1
Treatment 2: hereditary: O = 10; E = 1.37; O/E = 7.3 (95% CI 3.5 to 13.4) excess risk 3.1; non-hereditary: O = 6; E = 4.48; O/E = 1.3 (95% CI 0.5 to 2.9); excess risk 0.1

Note: Overall O/E by type of retinoblastoma: hereditary O/E =30 (95% CI 26 to 35); non-hereditary O/E = 1.6 (95% CI 0.7 to 3.1)

Outcome 2: cohort
Description:
Cumulative incidence (%) (SE) of second primary cancers in hereditary retinoblastoma patients at 50 years of follow-up

Treatment 1: hereditary: 58.3% (8.9%)
Treatment 2: hereditary: 26.5% (10.7%)

Note: Total cumulative incidence by type of retinoblastoma: hereditary 51.0% (SE 6.2%); non-hereditary 5.0% (SE 3.0%)

continued

Outcome 3: nested case–control
Description:
Risk (OR and 95% CI) of soft-tissue sarcoma by radiation dose to the site of the tumour (0–4.9 Gy was the reference category) (total 31 cases, 89 controls)

Treatment 1: 0–4.9 Gy (median control dose 1.6 Gy): 9 cases, 39 controls; OR 1.0
Treatment 2: 5.0–9.9 Gy (median control dose 7.2 Gy): 4 cases, 17 controls; OR 1.6 (95% CI 0.4 to 12.4)
Treatment 3: 10.0–29.9 Gy (median control dose 19.3 Gy): 10 cases, 18 controls; OR 4.6 (95% CI 1.7 to 24.8)
Treatment 4: 30.0–59.9 Gy (median control dose 39.6 Gy): 5 cases, 11 controls; OR 6.4 (95% CI 1.1 to 51.8)
Treatment 5: ≥ 60.0 Gy (median control dose 82.8 Gy): 3 cases, 4 controls; OR 11.7 (95% CI 0.0 to 162)

Outcome 4: nested case–control
Description:
Risk (OR and 95% CI) of soft-tissue and bone sarcoma by radiation dose to the site of the tumour (0–4.9 Gy was the reference category) (total 67 cases, 89 controls)

Treatment 1: 0–4.9 Gy (median control dose 1.7 Gy): 12 cases, 28 controls; OR 1.0
Treatment 2: 5.0–9.9 Gy (median control dose 7.2 Gy): 8 cases, 15 controls; OR 1.9 (95% CI: 1.4 to 2.6)
Treatment 3: 10.0–29.9 Gy (median control dose 19.6 Gy): 20 cases, 22 controls; OR 3.7 (95% CI: 2.8 to 4.5)
Treatment 4: 30.0–59.9 Gy (median control dose 40.1 Gy): 13 cases, 16 controls; OR 4.5 (95% CI: 3.7 to 5.6)
Treatment 5: ≥ 60.0 Gy (median control dose 97.7 Gy): 14 cases, 8 controls; OR 10.7 (95% CI: 8.6 to 14.5)

Updated data from Kleinerman *et al.* (personal communication, 2004)
The SIR was calculated and the observed number of confirmed new cancers compared to the expected number and 95% CI based on the Poisson distribution. The cumulative incidence of a second cancer was calculated with adjustment for competing risks

Cumulative incidence (%) of a second cancer 50 years after diagnosis:
Hereditary (n = 963), 36% (95% CI 30.8 to 41.1%); non-hereditary (n = 638), 5.7% (95% CI 1.4 to 10%)

Risk of second cancers in hereditary patients:
No radiotherapy: risk was increased almost 7-fold. With radiotherapy the risk was further increased by 3.1-fold (95% CI 2.0 to 5.3)

Risk of second cancers in non-hereditary patients:
Risk of breast cancer only was increased
No radiotherapy: SIR 2.8
Radiotherapy: SIR 10; observed number of cancers 3

Abramson (1998)[137]
Analysis was carried out on a subset of 816 patients from the original cohort who had been treated in the New York Hospital for whom age at initial radiation could be determined to the month. Kaplan–Meier survival curves were constructed with comparison made between patients treated with radiotherapy at <12 months of age, patients treated with radiotherapy >12 months of age, and patients who received no radiotherapy. The authors concluded that the risk of tumours in the field of radiation is heavily dependent on the age at which EBRT is given and may be acceptably small to the patient after the age of 12 months

OR, odds ratio; RR, relative risk; SIR, standardised incidence ratio.

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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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