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Is it worthwhile including observational studies in systematic reviews of effectiveness?

The experience from a review of treatments for childhood retinoblastoma

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Background

Retinoblastoma is a rare malignant tumour of the retina and usually occurs in children under two years old. It is an aggressive tumour that can lead to loss of vision and, in extreme cases, death. The prognoses for vision and survival have significantly improved with the development of more timely diagnosis and improved treatment methods. Important clinical factors associated with prognosis are age and stage of disease at diagnosis. Patients with the hereditary form of retinoblastoma may be predisposed to significant long-term complications.

Historically, enucleation was the standard treatment for unilateral retinoblastoma. In bilateral retinoblastoma, the eye with the most advanced tumour was commonly removed and the contralateral eye treated with external beam radiotherapy (EBRT). However, EBRT may be associated with the risk of serious long-term complications. There has been an increasing trend in the use of chemotherapy and local conservative treatments such as cryotherapy, photocoagulation and thermotherapy and a decrease in the use of radiotherapy and enucleation, where possible.

Objective

- To conduct a systematic review of the evidence-base for treatments for retinoblastoma.
- To consider the problems and benefits of including observational studies in a systematic review of the clinical effectiveness of treatments for retinoblastoma.

Methods

- Seventeen electronic databases were searched from inception to April 2004.
- Studies of participants diagnosed with childhood retinoblastoma were eligible for inclusion. Any intervention, or combination of interventions, 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.
- Two reviewers independently assessed titles and abstracts and full papers.
- One reviewer carried out data extraction and quality assessment and this was checked by a second reviewer.
- A narrative synthesis was conducted.

Results

- Thirty-one studies met the inclusion criteria. Apart from one study where some of the participants were randomised, only observational comparative studies were identified. Twenty-seven studies were retrospective.
- The studies were diverse.
- Most of the studies investigated EBRT or chemotherapy (see Figure). There were very few studies available on local 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. No studies compared different local treatments.
- Overall there were considerable problems with quality (see Table). Without randomised allocation there was a high risk of selection bias in all studies. Studies were also susceptible to detection and performance bias, with the retrospective studies particularly susceptible as they were less likely to have a study protocol specifying the intervention and outcome assessments.
- Due 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.

Figure 1: Mapping of included studies

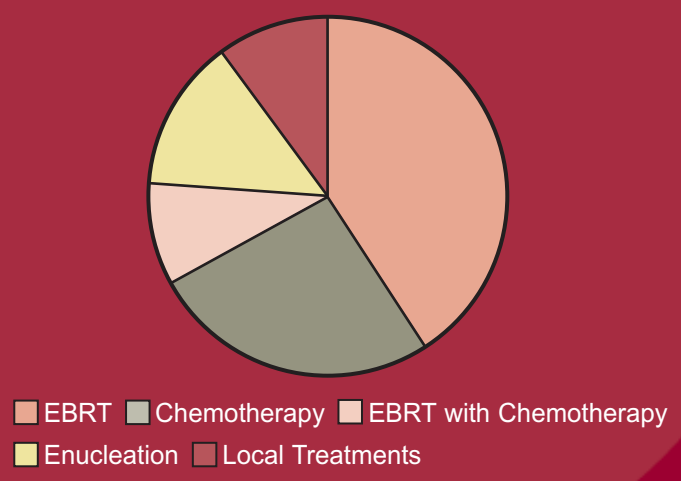

Table 1: Summary of study quality

Quality criteria	Studies meeting criteria	Comments
Description of assignment to intervention	n=14	Allocation was on the basis of disease severity, time period in which treatment was given, the clinic which provided the treatment or generally the treatment protocol in use.
Groups balanced by design	n=2	
Identification of relevant prognostic variables	n=21	Generally the only variable reported was Reese-Ellsworth classification or type of retinoblastoma.
Matched for relevant prognostic variables or effect of any group difference evaluated in a valid analysis	n=4	Some studies also reported outcomes by Reese-Ellsworth classification
Intervention groups comparable at baseline	n=4	In five studies there was evidence that groups were not comparable and in the remaining studies it was unclear or the relevant information was not reported
Number of patients lost to follow-up reported and rates similar across groups	n=2	Twenty-four studies included only patients on whom follow-up information was available. In four studies loss to follow-up was reported only for both treatment groups combined. In one study rates were reported for both groups but loss to follow-up was not similar across groups.
Follow-up period reported for both treatment groups	n=13	Mainly through use of Kaplan-Meier analysis
Analyses adjusted for different lengths of follow-up	n=10	
Follow-up long enough for the outcomes to occur	n=20	
Treatment clearly specified	n=12	
Clearly defined criteria for measuring outcomes	n=15	

Review conclusions

- The conclusion of the review was that good quality randomised controlled trials assessing the effectiveness of different treatment options for childhood retinoblastoma are required.
- Where controlled trials are not feasible, only high quality prospective, non-randomised studies should be given consideration, due to the generally higher risk of bias in retrospective studies.

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Was it worthwhile including observational studies?

- Stricter study design inclusion criteria would have led to the same conclusions in a more efficient way.
- It could be argued that it was inappropriate to include observational studies of treatment interventions in a systematic review due to the potential for bias.
- However the review would have been less comprehensive. Specific problems with the study designs used in this field were identified. We were able to make specific recommendations for improvement. Hopefully this will be useful for clinicians evaluating treatments for retinoblastoma.
- This review is currently being updated as a Cochrane review. Only controlled studies will be eligible for inclusion. It is unlikely that any studies will be found that meet these stricter inclusion criteria.

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