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Does chemotherapy affect the visual outcome in children with optic pathway glioma? A systematic review of the evidence

Lucas Moreno [a,*], *Francisco Bautista* [a], *Sue Ashley* [b], *Catriona Duncan* [a], *Stergios Zacharoulis* [a]

[a] *Department of Paediatrics, The Royal Marsden NHS Foundation Trust, Sutton, UK*
[b] *Department of Statistics, The Royal Marsden NHS Foundation Trust, Sutton, UK*

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ABSTRACT

Introduction: Overall prognosis for optic pathway glioma (OPG) in children is excellent. Little is known, however, about the effect of chemotherapy on visual outcome of these patients.
Material and methods: A systematic review of the literature was carried out to identify all studies published in PubMed, EMBASE and Cochrane Library between 1990 and 2008 reporting visual outcome in children with OPG after chemotherapy. Studies were included when they included 10 or more children with OPG, main treatment was chemotherapy and visual outcome was described. Cochrane guidelines for meta-analysis of non-randomised clinical trials were followed and levels of quality were assigned.
Results: Eighty-five potentially relevant publications were retrieved for detailed evaluation and only 8 were included. The review revealed 0 randomised controlled trials, 0 non-randomised controlled trials, 3 (37.5%) single-arm trials (1 multi-institutional and 2 single institution trials) and 5 (62.5%) retrospective series. All studies achieved a level of evidence of 4 according to CEBM classification (case-series and poor quality cohort and case-control studies). Only 25 of 174 children experienced improvement in vision after chemotherapy (14.4%), responses ranged from 0% to 45.5%. Vision was stable in 82 children (47.1%, range 27–100%). No study documented the duration of the visual response.
Discussion: Published studies on childhood low grade gliomas have not shown satisfactorily whether chemotherapy improves outcome of vision in children with OPG. Based on our systematic review it appears that treatment with chemotherapy does not improve resulting vision in the majority of children with OPG. The data available does not allow us to assess whether vision is stabilised sufficiently prior to treatment with radiotherapy.

1. Introduction

Low grade gliomas (LGG) are the most common paediatric brain tumours, accounting for 35–50% of all central nervous system neoplasms,[1] and the optic pathway is commonly affected. Patients with optic pathway gliomas (OPGs) have an excellent overall survival yet can still experience progressive disease and significant visual impairment.[2]

Children with OPG are frequently diagnosed after visual deficits are noted; other symptoms at presentation include proptosis or symptoms of hypothalamic syndrome. Approximately a third of patients with OPG are affected by

* *Corresponding author:* Address: The Royal Marsden Hospital, Department of Paediatrics, Downs Road, Sutton, Surrey SM2 5PT, UK. Tel.: +44 0208 661 34 55; fax: +44 0208 661 3617.
E-mail address: lucasmorenomr@hotmail.com (L. Moreno).
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neurofibromatosis 1 (NF1) and significant differences have been shown in terms of tumour biology, outcome, prognostic factors and neurocognitive deficits in this sub-group.[3]

Current standard recommendation is to start treatment when radiological/clinical progression or visual deterioration and/or impairment are detected. Options include different chemotherapy regimens as well as radiotherapy in older children.[4]

Visual function assessment in children is complicated and has age-specific limitations.[3,5] Controversy exists regarding criteria for initiation of treatment for children with optic pathway glioma and often, deterioration in vision is the only criterion used to initiate chemotherapy. The effect of chemotherapy on vision in optic pathway glioma is not well established. Controversial results from retrospective series have questioned whether the use of chemotherapy adds any benefit in terms of improvement in visual function.[5,6]

The aim of this study is to determine the impact of chemotherapy on the outcome of vision in children with optic pathway glioma based on the evidence provided by the literature.

2. Methods

2.1. Search strategy

To identify articles including therapeutic strategies for children with optic pathway glioma, PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez) was searched with the following strategy: ((('eye'[MeSH Terms] or 'eye'[All Fields] or 'optic'[All Fields]) and pathway[All Fields] and ('glioma'[MeSH Terms] or 'glioma'[All Fields])) or (low[All Fields] and grade[All Fields] and ('glioma'[MeSH Terms] or 'glioma'[All Fields]))) and ('therapy'[Subheading] or 'therapy'[All Fields] or 'treatment'[All Fields] or 'therapeutics'[MeSH Terms] or 'therapeutics'[All Fields]). This approach aimed to avoid the inclusion of studies of prognostic/biologic features, high-grade glioma or adult patients with low grade glioma.

Search was limited using the Advanced Search function in PubMed for articles published in children <18-years-old, in English between 1990 and 2008. We therefore avoided studies published in the 1980's when chemotherapy was rarely used to treat children with OPG and follow-up of these patients did not include MRI and rarely CT, thus not comparable with more recent studies.

To identify additional publications, search was performed in EMBASE and The Cochrane Library, references from articles included in the systematic review, review articles and current international cooperative LGG protocols (Children's Oncology Group (COG) and International Society of Paediatric Oncology (SIOP) collaborative trials) were reviewed. No communications to congresses or non-published data were searched for.

Search strategy was performed considering recommendations of the Cochrane Handbook for Systematic Reviews of Interventions version 5.0.2 for non-randomised clinical trials.[7]

Two authors (LM, FB) performed the literature search on OPG ('Potentially relevant publications identified and screened for retrieval' as per QUORUM statement) and selected papers reporting treatment strategies for LGG/OPG ('Potentially relevant publications retrieved for detailed evaluation' as per QUORUM statement). Abstracts and full text papers were reviewed to decide whether inclusion criteria were fulfilled. A third author (SZ) reviewed 'Potentially relevant publications retrieved for detailed evaluation' independently and blindly to peer-review the inclusion of papers.

2.2. Inclusion criteria

Studies were included if (i) children diagnosed with OPG were included (optic nerve – chiasmatic pathway gliomas), (ii) a minimum of 10 patients below 21 years of age were analysed, (iii) chemotherapy was the main intervention of the study and (iv) visual outcome was reported.

A minimum cut-off of 10 patients was decided prior to any literature search or analysis. It was estimated to be a reasonable sample size for any study with meaningful conclusions and statistical validity. This cut-off excluded small retrospective case-series from this review, thus preventing an excessive selection bias and the heterogeneity associated with these studies. Larger retrospective series were not excluded due to the scarcity of published data in chemotherapeutic treatment of OPG.

2.3. Quality assessment of studies

Studies were classified according to Cochrane Handbook for Systematic Reviews of Interventions version 5.0.2 recommendations[7] into randomised controlled trials (RCT), non-randomised controlled trials (NRCT), prospective cohort studies (PCS) and retrospective studies. The quality of the studies (non-randomised) was evaluated using eight items selected and modified from recently published guidelines developed by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons (AANS/CNS).[8] Studies satisfying more than 4 items were classified as high-quality (see Table 1).

Levels of evidence and grades of recommendation were assigned according to guidelines issued by Oxford Centre for Evidence-Based Medicine (version March 2009).[9]

2.4. Data extraction

From each publication, information was extracted regarding study design, inclusion criteria, reasons for initiating therapy, diagnostic and follow-up methods, NF1 status, chemotherapy schedule, outcome (response rate and progression-free survival), visual acuity (VA), visual fields (VF) and any further information about visual assessment after chemotherapy and during follow-up.

Additional data regarding visual outcome in children with OPG were extracted from 'Potentially relevant publications retrieved for detailed evaluation' that did not fulfil inclusion criteria but reported a detailed ophthalmologic assessment. These data were assessed separately from the systematic review.

2.5. Statistical analysis

Primary end-point was the number of patients experiencing visual acuity (VA) improvement as reported in the publication by each individual author after chemotherapy. Due to the heterogeneity of the included papers, the high proportion of

Table 1 – Studies fulfilling inclusion criteria.

Reference/score	*n*/NF1	Type of study	Median age (months)	Responses	PFS	Definition of progression	Visual assessment (patients)	Level of evidence
High-quality studies (satisfying more than 4 items)[a]								
Massimino et al.[16]	29/6	Prospective single institution	45	1CR, 23 PR, 10 SD[b]	73% (3-year)	Radiological progression (MRI) or neurological deterioration	Visual acuity, fields and evoked potentials (22)	4
Laithier et al.[17]	85/23	Prospective multi-institutional	17	23 SD, 51 PR	34% (5-year)	Radiological progression (MRI)	Visual acuity, fields and evoked potentials assessed (57)	4
Medium/low quality studies (satisfying 4 or less items)[a]								
Petronio et al.[11]	19/4	Retrospective single institution	28	10 PR, 5 SD	60% (5-year)	Radiological progression (CT/MRI), neurological or visual deterioration	Visual acuity (19)	4
Chamberlain and Grafe[12]	14/4	Prospective single institution	90	1 CR, 4 PR, 3 SD	ND	Radiological progression (CT/MRI) or neurologic deterioration	Visual acuity (14)	4
Janss et al.[13]	46/15	Retrospective single institution	27	11 PR, 9 SD	19% (5-year)	Radiological progression (MRI) or visual deterioration	Visual fields and visual acuity (27)	4
Silva et al.[14]	14/3	Retrospective single institution	10	8 PR, 1 SD	63% (5-year)	Radiological progression (MRI)	Visual acuity (14)	4
Mitchell et al.[15]	12/7	Retrospective single institution	60	1 PR, 9 SD	ND	Radiological progression (MRI/CT) or visual deterioration	Visual acuity (10)	4
Dalla Via et al.[3]	11/11	Retrospective single institution	26	ND	ND	ND	Visual acuity (11)	4
Total	230/73						174	

Abbreviations: ND: no data, CR: complete response, PR: partial response (includes minor responses), and SD: stable disease.

[a] For quality assessments eight items were evaluated: statistical analysis, detailed definition and reporting of response, detailed definition of eligibility criteria, presence of other confounding interventions (i.e. radiotherapy), statistical adjustment for confounding factors, detailed description of the intervention (s), recruitment for < or $\geqslant$10 years and detailed description of follow-up. Adapted from Ref. [8].

[b] Reported responses from 34 children with low grade glioma (including 29 with optic pathway tumours).

retrospective series and the lack of valid comparison groups among the different studies, meta-analysis and Maentel–Haensel test were not performed. The total proportion of patients experiencing visual acuity improvement in the included studies was calculated without confidence intervals. This calculation aimed to provide an orientation to clinicians but in no case aimed to perform a statistical analysis as this was deemed impracticable.

PRISMA and Cochrane guidelines for reporting meta-analysis were followed to ensure the quality of report.[7,10]

3. Results

Search strategy yielded 757 articles, 68 of them reported treatment strategies for LGG/OPG. Seventeen additional papers were included from search of the references, non-systematic reviews and current collaborative protocols (see Fig. 1). From the 85 retrieved publications, 77 did not fulfil inclusion criteria. Reasons for exclusion were as follows: language was not English (2 papers, 2.6%), inclusion of less than 10 children with OPG (39 papers, 50.6%), not focused on chemotherapy (prognostic factors, radiotherapy, surgery, observation or chemotherapy not specified; 18 papers, 23.4%) and insufficient information to quantify number of children with OPG (11 papers, 14.3%). Seven studies reporting treatment with chemotherapy for more than 10 children with OPG were excluded as visual outcome was not reported (9.1%). Of this group, six included visual deterioration as a criterion to start chemotherapy. In a significant proportion of cases, several inclusion criteria were not fulfilled. Eight studies met inclusion criteria and were analysed.[3,11–17]

3.1. *Assessment of quality of studies and level of evidence*

The review of the articles revealed: 0 randomised controlled trials, 0 non-randomised controlled trials, 3 (37.5%) single-arm trials (1 multi-institutional and 2 single institution trials) and 5 (62.5%) retrospective studies.

Despite the lack of randomised controlled trials in the review, two studies were graded as high-quality studies (Massimino and Laithier). Both of them were prospective studies, sample size was large in comparison with similar studies (29 and 85 patients, respectively) and the interventions and population were clearly defined (see Table 1) with detailed statistical analysis. The study from Massimino et al. studied the response of children with low grade glioma to a cisplatin-based regimen as an alternative to standard carboplatin-based regimens. Laithier et al. reported a protracted chemotherapy regimen designed to avoid or delay the use of radiotherapy in younger children with different histological diagnoses, in a large national collaborative study. The remaining six studies were considered of lower quality. They were retrospective or uncontrolled studies or data on inclusion, assessment and follow-up were inaccurately reported.

All studies achieved level 4 (case-series and poor quality cohort and case-control studies) according to CEBM classification.[9]

3.2. *Studies characteristics*

Table 1 summarises the characteristics of included publications. A total of 230 children with OPG were analysed in those 8 publications, 73 of them diagnosed of NF1 (31.7%). Median age at start of chemotherapy ranged from 17 to 90 months, and was below 36 months for 6 studies (75%).

Chemotherapy regimens comprised carboplatin monthly, carboplatin/vincristine (2 studies), 6-thioguanine, procarbazine and CCNU (TPCV) or nitrosourea-based, cisplatin/etoposide, oral etoposide, vincristine/actinomycin and SFOP (Société Française d'Oncologie Pédiatrique) BabyBrain.

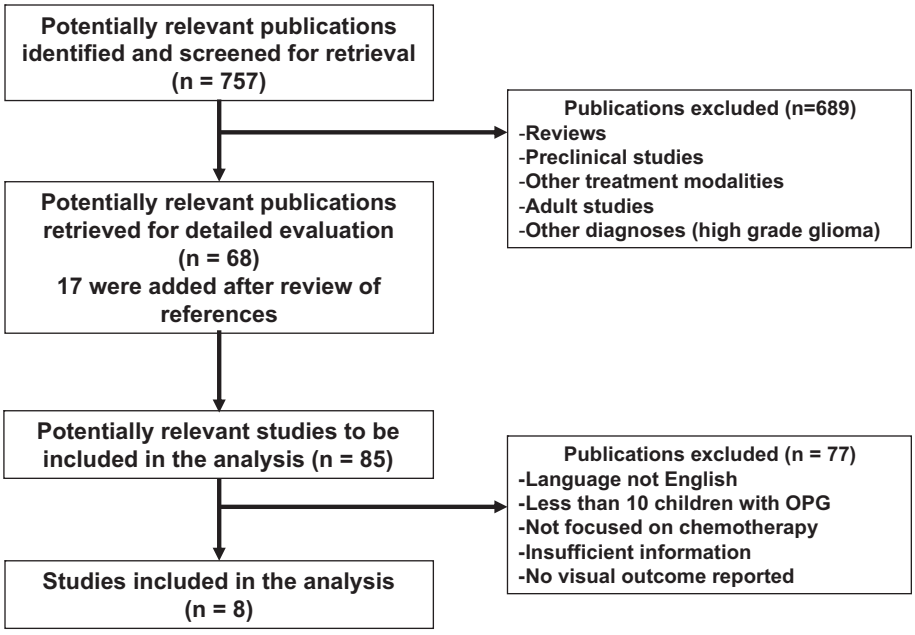

Fig. 1 – Flow diagram reporting results of the systematic review. Adapted from the QUality Of Reporting Of Meta-analyses (QUOROM) statement as no meta-analysis was performed in this study.

Objective radiologic responses ranged from 8.3% to 82.8% in the different studies (see Tables 1 and 2). Five-year progression-free survival ranged from 19% to 93%.

In all studies deteriorating vision was a criterion to start chemotherapy. Three studies specified the methodology and frequency of ophthalmologic follow-up. Only 2 studies including up to 28 patients (16.1%) provided necessary information to separate visual outcome for NF1 versus non-NF1 patients.[3,12]

3.3. *Visual outcome after chemotherapy*

In total, of the 174 children, 25 (14.4%) experienced an improvement in vision following chemotherapy, 82 (47.1%) remained stable and 67 (38.5%) experienced deterioration of their vision following chemotherapy. The range of improvement in vision was variable (0–45%) with only small number of patients reported (Table 2). No study documented the duration of the visual response, only median survival until radiological progression or last follow-up was provided.

A summary of other studies providing information about visual outcome in OPG is provided in Table 3; neither of them fulfilled the inclusion criteria of our study.[5,6,18–24]

4. Discussion

Optic pathway glioma is a highly curable disease with 5-year overall survival above 90%.[1,25] Visual outcome of this group of children has only been evaluated as an end-point in recent years.

Lengthy chemotherapy regimens are currently being used to treat patients with OPG in an attempt to improve or stabilise their vision. The justification for using long and potentially toxic therapy, however, has not been well described. Chemotherapy is used for a wide range of indications, including progressive disease in children younger than 8 years and all NF1 patients.

There are several limitations to our study that deserve discussion. First, the search strategy aimed to identify potential studies in children with optic pathway glioma treated with any form of chemotherapy. As the term ‘glioma’ is highly non-specific (the search ‘glioma’ in PubMed yielded more than 50,000 publications) some limitations to the search were added to detect children with low grade tumours arising in the optic pathway. It is therefore possible that these limits have hampered the sensitivity of the search, although references and other guidelines were searched.

Second, because of the heterogeneity of the studies statistical analysis was not performed. The authors decided to report the proportion of patients experiencing visual improvement in the eight selected studies. This proportion does not have any statistical value as the rates of visual improvement in the different studies ranging from 0% to 45.5% illustrate.

Third, the groups of patients differed among different studies with a tendency to treat younger children with chemotherapy, and some studies were specifically directed to infants.[14,17] As radiotherapy has been established for longer as a therapeutic modality for children with brain tumours and currently is used only to treat older non-NF1 children, this poses an additional source of bias to the analysis when comparing the results of chemotherapy with those of children receiving radiotherapy.

The results of this systematic review show that published studies on childhood low grade gliomas have not clarified whether chemotherapy improves visual outcome in children with OPG or the duration of stabilisation. Several large and multi-institutional prospective cohorts of children with LGG were identified but the majority were excluded for our analysis. Reasons for exclusion were small number of children with OPG, publications not analysing chemotherapy schedules or insufficient information to identify the number of children with OPG. We found that only 8 publications reported visual outcome, gathering up to 174 children from 1990 to 2008.

It also proved extremely difficult to classify the level of evidence of these cohorts provided all of them are single-arm studies. On this basis, according to current guidelines[9] they should all be classified as level 4, case-series (and poor quality cohort and case-control studies). No statistical comparisons between interventions have been made in any included study, not even with historical controls and for this reason the quality of the evidence is weaker.

In our systematic review only three studies reporting visual outcome were prospective, two of these were evaluated as high-quality. As described above, conclusions from these studies must be drawn carefully.

Unfortunately, due to a lack of data on ophthalmological follow-up and visual outcome, large prospective studies in children with low grade glioma which constitute the basis of

Table 2 – Responses to chemotherapy.

Reference	Schedule	Objective radiological responses (%)	Improving vision (%)	Stable vision	Deteriorating vision	Total
Massimino et al.[16]	Cisplatin–etoposide	24 (82.8)	10 (45.5)	7	5	22
Laithier et al.[17]	BabyBrain SFOP	51 (60)	2 (3.5)	16	39	57
Petronio et al.[11]	Nitrosurea based/TPCV	10 (52.6)	2 (10.5)	14	3	19
Chamberlain and Grafe[12]	Oral etoposide	6 (42.8)	0	14	0	14
Janss et al.[13]	Vincristine–actinomycinD	11 (23.9)	5 (18.5)	14	8	27
Silva et al.[14]	Carboplatin–vincristine	8 (57.1)	2 (14.3)	12	0	14
Mitchell et al.[15]	Carboplatin monthly	1 (8.3)	4 (40)	3	3	11
Dalla Via et al.[3]	Carboplatin–vincristine	ND	0	2	9	11
Total			25 (14.4)	82	67	174

Table 3 – Visual outcome in OPG: non-included studies. All of them are retrospective series. RT: radiotherapy.

Reference	*n* (NF1)	Intervention	Outcome
Lund and Skovby[18]	16 (16)	11 had RT, 1 had chemotherapy	Vision improved in 10% of eyes, stable in 55% and worse in 35%
Sutton et al.[19]	33 (4)	29 had RT, 18 had chemotherapy	Five patients functionally blind, 22 remained stable
Listernick et al.[20]	9 (9)	All had carboplatin monthly	Two out of 9 improved vision
Gayre et al.[5]	42 (23)	Chemotherapy/radiotherapy, not specified	Visual acuity remained stable in non-treated patients. In treated patients, vision deteriorated in the worse eye, while stable in better eye
Demaerel et al.[21]	9 (5)	All had vincristine–carboplatin	Six maintained vision, 3 deteriorated
Khafaga et al.[22]	50 (18)	28 had RT, none had chemotherapy	Vision improved in 7, unchanged in 31 and deteriorated in 6 patients. No data detailing outcome in the group receiving RT
Tow et al.[6]	47 (22)	33 had RT, 8 had chemotherapy	89–100% of not treated patients maintained an acceptable vision at follow-up. Only 10–40% of treated children maintained acceptable vision in the affected eye at follow-up
Thiagalingam et al.[23]	54 (54)	All had visual impairment at diagnosis (31 symptomatic, 11 severe), 7 had RT, 2 had chemotherapy, 3 had both	16.7% had bilateral moderate/severe visual impairment but the rest kept acceptable vision in at least one eye
Suarez et al.[24]	19 (1)	17 had visual symptoms at diagnosis, 14 received surgery, 5 radiotherapy, 2 chemotherapy	Out of 12 survivors, 10 had reduced vision and 2 became blind

current standard treatment were not included in this analysis.[26–28]

This study showed how despite difficulties assessing visual function in children, more information is needed from collaborative studies. Several large studies used visual deterioration as a criterion to start chemotherapy, although visual outcome was not then reported. Only three studies specified the methodology and frequency of ophthalmologic follow-up; and there were different definitions of progression used in OPG. Neurological and visual deterioration were inconsistently used as progression criteria among included studies. Several large studies including children with OPG have defined progression based only on radiological criteria[26–28] while others based progression on radiological, neurological and visual evaluations.[29,30]

There was insufficient information to allow us to differentiate between patients with or without neurofibromatosis 1 (NF1) in more than 70% of papers, accounting for 85% of the patients.

There are, however, several retrospective series evaluating the visual outcome in children with OPG although no analysis of the treatment strategy has been performed. Children with NF1 have better visual outcome compared to non-NF1 patients. Of note, children with stable tumours under observation have better visual outcome compared to the ones requiring adjuvant treatment.[5,6] In most cases, vision in the more affected eye deteriorates but remains stable in the better eye with an acceptable vision. Less than 20% of cases experience severe bilateral visual deterioration or are declared functionally or legally blind.[19,23,24]

Based on our systematic review it seems that treatment with chemotherapy does not improve visual outcome in the majority of children with OPG. When we considered the total number of patients in whom information about visual outcome is available, less than 15% of cases had improved vision after chemotherapy and it deteriorated in 40%. It appears that even though the tumours are chemo-sensitive, the visual deterioration in the majority is irreversible despite this strategy. The radiological responses in the different studies ranged from 8% to 80% and did not appear to correlate with the proportion of patients experiencing visual improvement.

It is known that there are significant differences between NF1 and non-NF1 children. We attempted to separate the two cohorts in our review but data were not available. While overall prognosis for the former group is better, other aspects of neurofibromatosis can influence visual outcome. It is therefore important to have separate analysis and stratification for patients with NF1 evaluating their vision outcome as an endpoint. In spite of the very small number of patients included in each study, best responses in our review were achieved by the Italian cisplatin–etoposide regimen; up to 45% of children improved their vision in this cohort. Response to carboplatin-based regimens was variable (8–40%), but it must be considered that larger series with carboplatin–vincristine regimen[26,27] were not included in this analysis for lack of specific data. The largest good quality series included in our analysis[17] included 74 children treated with SFOP BabyBrain protocol. The younger age of this population (median age 17 months) and the different methodology of evaluating vision might have also influenced the visual outcome. Eleven children (14.8%) were blind as a result of their OPG and only 18 of them (24.3%) had a relatively preserved vision. It must be underlined that in more than two thirds of the median age was below 3 years.

Whether the use of chemotherapy stabilises the vision for a sufficient period prior to the use of radiotherapy could not be addressed from the available data. Several retrospective series have reported visual outcome after radiotherapy: 24–36% of the patients experienced improvement[1,25,31–33]

and 42–92% of children experienced stabilisation.[1,25,31–35] The responses appear to be better after radiotherapy, but the comparison of efficacy between these two treatment modalities cannot be valid as the patients' characteristics are not comparable. Given the issues with long term toxicity of radiation therapy but taking into consideration the ineffectiveness of chemotherapy and the advent of new radiotherapy modalities perhaps careful prospective clinical study design is required for non-NF1 patients.

The results of the recently closed and ongoing COG and SIOP trials are awaited and hopefully some of these issues will be answered. In conclusion there is weak evidence that chemotherapy (14.4%) improves vision, the achieved level of recommendation from this review is D.[9] Stabilisation is more likely but in the absence of randomised trials and without stratifying for neurofibromatosis it is very difficult to differentiate the chemotherapy effect versus the biology and natural course of these tumours. Globally accepted standard treatment initiation criteria, visual assessment methodology and long term follow-up and randomised trials are urgently needed.

Conflict of interest statement

None declared.

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