available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

Prognostic factors for progression of childhood optic pathway glioma: A systematic review

Enrico Opocher[a], *Leontien C.M. Kremer*[a], *Liviana Da Dalt*[b], *Marianne D. van de Wetering*[a], *Elisabetta Viscardi*[c], *Huib N. Caron*[a], *Giorgio Perilongo*[b,*]

[a]*Department of Pediatric Oncology, Emma Children's Hospital/Academic Medical Center (AMC), University of Amsterdam, The Netherlands*
[b]*Division of Pediatrics, Department of Pediatrics, University Hospital of Padua, Via Giustiniani 3, 35128 Padua, Italy*
[c]*Division of Hemato-oncology, Department of Pediatrics, University Hospital of Padua, Italy*

ARTICLE INFO

Article history:
Received 4 January 2006
Accepted 10 February 2006
Available online 30 June 2006

Keywords:
Optic nerve glioma
Optic chiasm
Astrocytoma
Neurofibromatosis type 1
Hypothalamic neoplasm

ABSTRACT

A systematic literature review was carried out to evaluate best existing evidence on prognostic factors for progression of childhood optic pathway glioma. Databases were searched for relevant articles and articles selected independently by two authors. Information about study design, population, treatment, outcome and prognostic analysis were abstracted and the quality of each article was assessed. A total of 23 articles met the inclusion criteria. Many studies had important methodological limitations, regarding external and internal validity. Eleven studies evaluated possible prognostic factors in a multivariate analysis. Three high-quality studies indicated age < 1 year as an independent prognostic factor for a worse progression-free survival. Three studies with multivariate analysis, including one high-quality study, found that children with neurofibromatosis type 1 (NF-1) have a better progression-free survival than those without NF-1. Two studies with multivariate analysis found tumour site to be a prognostic factor, both with some methodological limitations. In conclusion, this systematic review demonstrates that only a few of the prognostic factors proposed have been proven to be clinically relevant. Age < 1 year is a clear and independent prognostic factor for progression-free survival. Other prognostic factors, such as NF-1, tumour site and others, are suggested, but are still without solid evidence and need further high-quality studies to be clearly proven.

1. Introduction

Childhood low-grade glioma (LGG) is the most common paediatric central nervous system (CNS) neoplasm. Despite multiple studies on LGG, spanning many years, many questions regarding its natural history, optimal management, response to treatment and prognostic factors remain unanswered. This is particularly true for those LGGs not amenable to complete surgical resection. Optic pathway glioma (OPG) represents a prototype of this latter group of LGG. It is a relatively homogeneous group of neoplasms, in terms of tumour site and histological appearance.[1] OPGs are confined to the structures of the visual pathway and, histologically, they are almost uniformly pilocytic astrocytoma (WHO grade I). Children affected by neurofibromatosis type 1 (NF-1) are predisposed to develop OPG: the prevalence of NF-1 in childhood OPG varies between 20% and 50%, depending on series, while the prevalence of OPG in the NF-1 population varies between 1.5% and 15%, with only a few of them being symptomatic.[1] Many of these tumours show prolonged indolent phases, while others

* *Corresponding author:* Tel.: +39 049 8213579; fax: +39 049 8213510/02.
E-mail address: giorgio.perilongo@unipd.it (G. Perilongo).
0959-8049/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2006.02.022

progress rapidly and/or may have an erratic growth pattern. Spontaneous tumour regressions have also been documented.[2] Only OPGs that show growth potential or cause severe clinical symptoms are candidates for therapy. Many different factors, such as age at diagnosis (or at start of treatment), tumour site along the optic pathway, and NF-1 status, have been suggested as possible predictors of tumour progression, in terms of visual loss and/or neuro-radiological tumour enlargement. Considering existing uncertainties about the natural history of OPG and the need to select patients appropriately for treatment, it is becoming more urgent to investigate prognostic factors for tumour progression. With this purpose in mind, a systematic review of the published literature was carried out to appraise and summarise best existing evidence on clinically relevant prognostic factors and risk for progression of childhood OPG.

2. Materials and methods

2.1. Literature search

A search strategy was drawn up to identify published studies including children with OPG and any sort of analysis of prognostic factors. The following electronic databases were searched for articles: PubMed from 1966 to October 2005, EMBASE from 1980 to October 2005 and CENTRAL (the Cochrane central register of controlled trials) from 1999 to November 2005. The search strategy is presented in Table 1. Bibliographies of reviews and other relevant studies were searched for additional articles; furthermore, experts in the fields were asked for unpublished studies. Inclusion criteria were: (i) original studies; (ii) published in English, Italian, Dutch, German or French; (iii) series of more than 20 patients with mean age < 18 years; (iv) diagnosis of OPG based on magnetic resonance imaging (MRI) or computerised tomography (CT) scan; (v) management options including: no treatment, surgical resection in less than 50% of study population, radiotherapy, chemotherapy or combined treatments; (vi) clinical, visual and/or radiological progression as the outcome; (vii) a prognostic factor analysis performed. Cohorts of LGG or pilocytic astrocytoma were eligible if OPG represented more than 50% of the entire study group. An initial identification of possibly relevant articles was independently undertaken by two of the authors (EO and LK). After this first screening, relevant articles were retrieved and submitted to a second selection, based on the full-text reading. Reasons for excluding articles were clearly stated by the authors. Inter-observer agreement was calculated for both of the selection steps. In case of disagreement, articles were re-examined and discussed until consensus was achieved. In case of double publication, only the article with multivariate analysis of prognostic factors was included. If a multivariate analysis was not performed, the more recently published article was included.

2.2. Data extraction

From each selected article, detailed information on study design, setting, population, follow-up, intervention, outcome, prognostic factor analysis and risk estimate were abstracted by two of the authors (EO and GP). Progression was coded as progression rate, progression-free survival (PFS) or time-to-progression. Data extraction was performed using standardised forms. Data on the whole cohort of LGG patients in the original study group were collected if data on OPG study group were lacking. A meta-analysis of prognostic factors was not performed, because of the expected heterogeneity of study population, treatment modalities and the variety of prognostic variables considered. Identification of significant prognostic factors was based on a P-value $\leqslant 0.05$ and risk estimate expressed as relative risk (RR) or hazard ratio (HR), with confidence interval (CI).

2.3. Validity of the articles

To determine the validity of the selected articles, two authors (EO and LK) assessed the external and internal validity of the composition of the study group, the follow-up and outcome assessment, the prognostic analyses and risk estimates of each study. Validity criteria were defined as met (+), unmet (−), not mentioned (nm) and a validity score of each article was not performed. In case of disagreement, articles were re-examined and discussed until consensus was achieved. The validity assessment was based on a pre-existing checklist for observational studies, according to evidence-based

Table 1 – Search strategy for MEDLINE/PubMed

1. optic nerve gliom* [Text Word] OR optic nerve tumour* [Text Word] OR optic nerve tumour* [Text Word] OR "optic nerve neoplasms" [MeSH Terms] OR optic nerve neoplasms [Text Word]
2. "neurofibromatosis 1"[MeSH Terms] OR neurofibromatosis 1[Text Word] OR "astrocytoma" [MeSH Terms] OR pilocytic astrocytoma [Text Word] OR "hypothalamic neoplasms"[MeSH Terms] OR hypothalamic neoplasms [Text Word] OR "glioma"[MeSH Terms] OR glioma [Text Word] OR gliom* [Text Word]
3. "optic nerve" [MeSH Terms] OR optic nerve [Text Word] OR optic nerves [Text Word] OR "optic chiasm" [MeSH Terms] OR optic chiasm [Text Word] OR optic tract* [Text Word] OR optic pathway* [Text Word]
4. 2 AND 3
5. 1 OR 4
6. infant OR infants* OR newborn OR newborn* OR baby* OR babies* OR neonate* OR prematur* OR preterm* OR child OR child* OR preschool OR schoolchild* OR schoolage* OR adolescent OR adoles* OR teen* OR youth* OR minor* OR underage* OR juvenile* OR boy* OR girl* ORtoddler* OR puber* OR paediatric* OR paediatric OR paediatric* OR primary school* OR elementary school* OR high school* OR kindergart*
7. 5 AND 6

* Truncate word.

Table 2 – Data description summary

Author/ year	Kovalic 1990[6]	Jenkin 1993[7]	Deliganis l996[8]	Janss l996[9]	Regueiro 1996[10]	Erkal 1997[11]	Prados l997[12]
Study characteristics							
Country / setting	USA, unicentre	USA, multicentre	USA, unicentre	USA, unicentre	Spain, unicentre	Turkey, unicentre	USA, unicentre
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Prospective single-arm trial
Time period	1977–1978	1985–1990	1985–1990	1977–1990	1967–1993	1973–1994	1984–1992
Patients' characteristics							
n patients	35 OPG	87 OPG	44 OPG	46 OPG	36 OPG	33 OPG	42 LGG (33 OPG)
Original study group	OPG treated with radiotherapy	Consecutvie OPG	Consecutive OPG	Children <5 years with OPG	OPG treated with radiotherapy	OPG treated with radiotherapy	Progressive LGG
Review study group	Whole cohort	Whole cohort	Whole cohort	Whole cohort	Whole cohort	Whole cohort	Whole cohort
Tumour site (Dodge)	D-I (15%), D-II (24%), D-III (61%)	D-I (22%), D-II (18%), D-III (60%)	D-I (19%), D-II (65%), D-III (15%)	D-II (59%), D-III (41%)	D-I (17%), D-II or D-III (83%)	D-I (12%), D-II (61%), D-III (27%)	D-III (100%)
Age at diagnosis	Median 4 years	Median 4 years	Mean 5.2 years	Mean 34 months	Median 6 years	Median 7 years (2-28)	Mean 5 years
% of NF-1 patients	33%	43%	36%	33%	25%	18%	15%
Intervention							
Type of intervention	100% radiotherapy	43% radiotherapy 11% resection	63% radiotherapy 33% chemotherapy	70% chemotherapy ACT-D-vincristin 13% radiotherapy	100% radiotherapy	100% radiotherapy	100% chemotherapy
Follow-up							
Follow-up length	Median 12.3 years (2–31 years)	Median 11.55 years	Mean 7.8 years	Median 72 months	Median 9.6 years	Mean 13.6 years	Median 45 months
Prognostic analysis							
Prognostic variables	Age at diagnosis, surgery, RT, gender, race	Age eat diagnosis, NF-1 , tumour site, sex, RT, Surgery	NF-1	NF-1	Age, NF-1, hydro cephalus, neurol.deficts, RT dose,	NF-1, tumour site	Age, sex, histology
Statistical methods	Multivariate Cox	Multivariate Cox	Chi -squared test	χ^2 test	Multivariate Cox	Univariate-log	Multivariate Cox
Outcome (definition)	PFS (radiological progression only)	PFS (nm)	Frequency, time to progression (clinical and/or radiological)	Frequency of progression (clinical or radiological)	PFS (radiological or clinical progression)	PFS (nm)	Time to progression (radiological only)
Risk estimate	nm	nm	nm	nm	RR	nm	RR

(*continued on next page*)

Table 2 – *continued*

Packer 1997[13]	Chan 1998[14]	Shroder l999[15]	Grill 2000[16]	Grabenbauer 2000[17]	Komreich 2001[18]	Gayre 2001[19]	Balcer 2001[20]	Massimino 2002[21]
USA, unicentre	UK, unicentre	Germany, unicentre	France, unicentre	Germany, unicentre	Israel, multicentre	USA, unicentre	USA, unicentre	Italy, multicentre
Prospective single-arm trial	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Prospective single-arm trial
1989–1993	1977–1994	1994–1996	1980–1998	1975–1997	1985–1996	1970–1998	1992–1999	1991–2000
78 LGG (58 OPG)	69 OPG	25 OPG	106 OPG	25 OPG	91 OPG	42 OPG	43 OPG	34 LGG (29 OPG)
Progressive LGG	Treated OPG selected based on their prognosis	Consecutive OPG	Progressive OPG	OPG treated with RT	Consecutive OPG	All referred OPG	Consecutive OPG	Progressive LGG
Whole cohort	Whole cohort	Childhood OPG	35 Untreated OPG	Whole cohort	Untreated OPG	Untreated subgroup	Whole cohort	Whole cohort
D-II or D-II	D-I (12%), D-II or D-III (88%)	D-I (45%), D-II (25%), D-III (30%)	Unclear	D-I (8%), D-II (32%), D-III (60%)	D-III (50%)	Unclear	D-I (9%), D-II (41%)D-III (50%)	D-II or D-III only
Median 3 years	Unclear	Mean 4.5 years	nm	nm	Mean 5 years	Mean 11.1 years	Median 3 years	Median 45 months
20%	40%	100%	60%	12%	50%	55%	100%	25%
100% chemotherapy (carbo-vincristine)	19% RT; 9% Chemotherapy; 25% surgery	18% surgery	No	100% radiotherapy	No	No	nm	100% chemotherapy (cisplatin-etoposide)
Median 30 months	Unclear	Median 6.5 years	Median 7 years	Median 9 years (1.5–23)	nm	Mean 108 months	Median 3 years	Median 44 months
Age, NF-1 , histology	Age at diagnosis, NF-1, tumour site, RT, chemotherapy	Age at diagnosis	NF-1	Age, NF-1, tumour site, surgery, RT dose	NF-1	NF-1	Tumour site	Age at start treatment, NF1
Univariate-log PFS (radiological progression only)	Multivariate Cox PFS(nm)	χ^2 test Frequency of progression (visual acuity loss)	χ^2 test Frequency of progression (visual loss)	Multivariate Cox PFS (radiological and clinical progression)	χ^2 test Frequency (radiological progression only)	χ^2 test Frequency (visual progression)	Multivariate Cox Frequency of progression (visual loss)	Univariate-log PFS (nm)
nm	HR	nm	nm	nm	nm	nm	nm	nm

Gururangan 2002[22]	Khafaga 2003[23]	Fouladi 2003[24]	Laithier 2003[25]	Gnekow 2004[26c]	Komotar 2004[27]	Perilongo 2006[28d]
USA, multicentre Prospective single-arm trial	Saudi Arabia, unicentre Retrospective	USA, unicentre Retrospective	France, multicentre Prospective single arm trial	German, multicentre Prospective study	USA, unicentre Retrospective study	Europe, multicentre Prospective single arm trial
1993–2000	1980–1995	1981–1999	1990–1998	1996–2002	1966–1996	1993–2000
81 LGG (51 OPG)	50 OPG	73 OPG	84 OPG	198 OPG	63 OPG	210 LOG (74% OPG)
Progressive LGG	OPG treated with Radiotherapy	Consecutive OPG	Progressive OPG	Consecutive OPG	Unclear	Progressive LGG

Whole cohort	Whole cohort	Whole cohort	Whole cohort	123 OPG treated with chemotherapy	Whole cohort	Whole cohort
D-II or D-III only	D-I(11%), D-II (14%), D-III (75%)	D-II (30%), D-III (70%)	D-I (4%),D-II (20%), D-III (75%)	D-II (17%), D-III (83%)	D-III (100%)	D-II or D-III only
Median 49 months	Median 4 years	Median 4.7 years	Median 17 months	Median 2.9 years (0.2–16)	Median 72 months	Median 35.6 months
30%	36%,	38%	27%	27%	No	21%
100% chemotherapy (carboplatin)	100% RT, 65% surgery	30% RT, 20% chemotherapy	100% chemotherapy (BBSFOP)[b]	100% chemotherapy (carbo-vincristine)	65% Chemotherapy + Radio therapy	100% chemotherapy (carboplatin-vincristine)
Median 55 months	Median 7 years (2.4–16.5)	Median 6.3 years	Median 6.5 years	Median 60 months	Un clear	Median 6.1 years
Age at diagnosis, NF1	Age at diagnosis, tumour site, NF1 , RT	Age at diagnosis, NF1, tumour site, UBOs[a], treatment	Age at start treatment, NF1, tumour site, response to treat.	Age at start treatment, NF1, tumour site, histology , diencephalic sdr	Histology (pilomyxoid astrocytoma)	Age art treatment, NF1, histology, surgery, response to chemoth
Univariate-log	Univariate-log	Multivariate Cox	Multivariate Cox	Multivariate Cox	Univariate-log	Multivariate Cox
PFS (clinical or radiological progression)	PFS (nm)	PFS (nm)	PFS (clinical and/or radiological progression)	PFS (clinical or radiological progression)	PFS-time (radiological only progression)	Multivariate Cox PFS (clinical and/or radiological progression)
nm	nm	nm	RR	HR	nm	HR

a – UBOs (Unidentified Bright Objects), areas of increased T2-weighted signal intensity on MRI, only seen in NF1 children.
b – BBSFOP, baby brain SFOP: chemotherapy regimen:carboplatin+procarbazine/etoposide+cisplatin/cyclophosphamide+vincristine.
c – Gnekow (2004) and Perilongo (2006) contain partially overlapping patients.
d – Perilongo (2006) (in press, by permission of the authors).

criteria[3,4] or other previous systematic reviews on prognostic factors[5] and was adjusted by the authors for the specific context. The validity of the study group was considered 'well-defined' if the number of patients, age at diagnosis, tumour site, diagnostic methods, percentage of NF-1 patients and type of intervention were clearly described. The study population was considered representative of the original source population if all or more than 90% of eligible patients were included. If patients were selected based on unclear or unstated criteria for starting treatment, or on their prognosis, they were considered as not representative of the original population. The validity of the follow-up was judged 'adequate' if mean or median follow-up time were of 5 years or longer. Follow-up was complete if the outcomes were assessed at the end of the follow-up period, for more than 90% of patients. The outcome was judged as 'well-defined' if the authors clearly defined progression as neuro-radiological tumour enlargement at serial MRI or CT scan (radiological outcome) and/or visual acuity loss (visual outcome) or presence of severe symptoms. An objective blind outcome was judged if the outcome assessment was performed without knowledge of any clinical or tumour characteristics. Prognostic analysis was judged as 'well-defined' if a risk estimate (RR or HR) was reported, and 'well-adjusted' if a multivariate analysis was carried out.

3. Results

3.1. Selection of articles

The results of the search strategy with different databases were matched and yielded 1363 potentially relevant articles. After the first selection 95 articles were retrieved for more detailed examination. After the second selection 21 articles met the review inclusion criteria.[6–26] Inter-observer agreement of the two-step selection was 96% and 97%, respectively. One further article was retrieved and included after searching the bibliographies[27] and one manuscript in press was included after asking experts.[28] In all, 23 articles were included in the systematic review.[6–28] Seventy-four articles were excluded for the following reasons: review article ($n = 4$), other languages ($n = 4$), series of less than 20 children with OPG ($n = 19$), mean age > 18 years ($n = 1$), no outcome of interest ($n = 12$), no prognostic factor analysis ($n = 30$), double publication ($n = 4$).

3.2. Description of the selected articles

Characteristics of the 23 included articles are presented in Table 2. Sixteen were retrospective and 7 prospective and a total of 1357 OPG patients were considered. Median age at diagnosis in different series varied between 17 months and 11.5 years and the percentage of NF-1 patients varied between 12% and 60%. Two series were composed exclusively of NF-1 patients[15,20] and one of non-NF-1 patients.[27] Median follow-up varied between 30 months and 12.4 years. Authors used different definitions for progression: 5 articles defined progression as neuro-radiological evidence of tumour enlargement only, and 4 as visual deterioration or appearance of other severe symptoms related to tumour growth, while only 8 articles considered both criteria. PFS was the main outcome

Table 3a – Multivariate analysis prognostic factors results

Author / year	Type of analysis	Type of outcome	Prognostic factors (variables) and risk estimate ('P' value)
Kovalic 1990[6]	Multivariate analysis	15 years PFS	• Age at diagnosis (>15 years versus <15 years): nm* **(P = 0.029)**[a] • NF-1 (+ versus –): nm* (P = 0.59) • Tumour site (D-I versus D-II versus D-III): nm* **(P = 0.052)** • Surgery (biopsy versus partial resection versus none): nm* (P = 0.51) • Race (white versus black) nm* (P = 0.06) • RT dose (>40 Gy versus <40 Gy) nm* (P = 0.08) • Gender (female versus male): nm* (P = 0.27)
Jenkin 1993[7]	Multivariate analysis	10 years PFS	• Age at diagnosis (>4 years versus <4 years): nm* (P = 0.40) • NF-1 (+ versus –): nm* **(P = 0.003)** • Tumour site (D-I/II versus D-III): nm* (P = 0.43) • RT (+ versus –): nm* **(P = 0.05)** • Primary resection (+ versus –): nm* (P = 0.19) • Sex (male versus female): nm* (P = 0.77)
Regueiro 1996[10]	Multivariate analysis	10 years PFS	• Age at diagnosis (>2 years versus <2 years): nm* (P = ns) • NF-1 (+ versus –): nm* (P = ns) • Neurology deficits (– versus +): nm* (P = ns) • RT dose (>50 Gy versus <50 Gy): nm* (P = ns) • Hydrocephalus (+ versus –): **RR = 6.65 (CI = 2.04–21.62) (P = 0.002)**
Prados 1997[12]	Multivariate analysis	Time to progression	• Age at treatment (higher versus lower): **RR = 0.81** (CI = nm) **(P = 0.004)** • Sex (male versus female): nm (P = ns) • Histology (PA versus others): nm (P = ns)
Chan 1998[14]	Multivariate analysis	PFS	• Age at diagnosis (0–3.5 years versus 3.5–6 years versus 6–15 years): **HR = 7.68** (CI = nm) **(P < 0.05)** • NF-1 (+ versus –): nm* **(P < 0.0005**, in a model with multiple covariates with age, chemotherapy and radiotherapy) • Tumour site (D-I versus D-II/D-III) = nm* (P = ns) • Radiotherapy (+ versus –): HR = 0.103 (CI = nm) (P = nm) • Chemotherapy (+ versus –): HR = 0.646 (CI = nm) (P = nm)
Grabenbauer 2000[17]	Multivariate analysis	PFS	• Age at diagnosis (1.5–10 years versus >10 years): nm* (P = 0.09) • NF-1 (+ versus –): nm* (P = ns) • Tumour site (D-I versus D-II versus D-III): nm* (P = 0.5) • RT dose (>45 Gy versus <45 Gy): nm* **(P = 0.04)** • Surgery (biopsy versus partial resection): nm* (P = 0.3)
Balcer 2001[20]	Multivariate analysis	Visual outcome (visual acuity loss)	• Age at diagnosis (nm): nm* **(P = 0.051)** • Tumour site (D-I/II versus D-III): nm* **(P=0.041)**
Fouladi 2003[24]	Multivariate analysis	6 years PFS	• Age at diagnosis (>2 years versus <2 years): nm* (P > 0.05) • NF-1 (+ versus –): nm* (P > 0.05) • Tumour site (D-II versus D-III): nm* (P > 0.05) • RT treatment (+ versus –): nm* **(P = 0.056)** • UBOs MRI lesions (+ versus –): nm* **(P = 0.015)**
Laithier 2003[25]	Multivariate analysis	3- years PFS	• Age at treatment (<1 years versus >1 years): **RR = 1.8 (CI = 1.02–3.02) (P = 0.047)** • NF-1 (+ versus –): **RR = 0.47 (CI = 0.22–0.99) (P = 0.035)** • Tumour site (D-III versus D-I /II): RR = 1.6 (CI = 0.84–3.0) (P = 0.15) • Response to chemotherapy (stable disease/objective effect versus partial/complete response): **RR = 2.6 (CI = 1.4–5.0) (P = 0.0029)**
Gnekow 2004[26]	Multivariate analysis	5 years PFS	• Age at treatment (1–4 years versus <1 years): **HR = 0.51 (CI = 0.26–1.02)**; (5–10 years versus <1 years): **HR = 0.20 (CI = 0.06–0.70)**; (>10 years versus <1 years): **HR = 2.8 (CI = 0.59–13.21) (P = 0.008)** • NF-1 (+ versus –): nm* (P = 0.09) • Tumour site (D-II versus D-III) = nm* (P = ns) • Histology (non-pilocytic versus PA): **HR = 23.67 (CI = 7.01–79.94) (P < 0.001)**; (clinical diagnosis versus PA): HR = 0.99 (CI = 0.48–2.02)

Table 3a – *continued*

Author / year	Type of analysis	Type of outcome	Prognostic factors (variables) and risk estimate ('P' value)
Perilongo 2006 (in press)[28]	Multivariate analysis	5 years PFS	• Age at treatment (1–5 years versus < 1 years): **HR = 0.44 (0.27–0.72)** (P = nm); (5–10 years versus < 1 years): **HR = 0.49 (CI = 0.26.0.90)** (P = nm) • NF-1 (+ versus –): nm* (P = ns) • Surgery (biopsy versus clinical diagnosis): **HR = 2.27 (CI = 1.37–3.77)** (P = nm) • Response to chemotherapy (complete/partial/minimal response versus stable disease): nm* (P = ns)

CI, 95% confidence interval; D–, Dodge's tumour site classification; Gy, Grey RT dose; HR, hazard ratio; LogMAR, minimum angle resolution; MRI, magnetic resonance images; NF-1, neurofibromatosis type 1; nm, not mentioned; ns, not significant; PA, pilocytic astrocytoma; PFS, progression-free survival; PMA, pilomixoyd monomorphous astrocytoma; RR, relative risk; RT, radiotherapy.
a In bold significant results.
* First term as the favourable prognostic variable.

measurement and was calculated from the date of starting therapy to the date of tumour progression in all the prospective studies, and from the date of OPG diagnosis to the date of tumour progression in all the retrospective studies. NF-1 status, age of patient and tumour site were the more common prognostic factors evaluated in these articles. In 11 articles a multivariate analysis was performed, in 6 articles a univariate log-rank analysis, and in 7 a χ^2 test comparison was used. A risk estimate for progression was evaluated in 3 articles as RR and other 3 as HR. In 5 prospective studies the results of prognostic analysis were based on results of the whole LGG population, because no separate results for OPG subgroup were available.[12,13,21,22,28]

3.3. *Prognostic factor analysis*

The results of the prognostic factor analysis are shown in Table 3(a and b). The prognostic value of age was evaluated with a multivariate analysis in 4 prospective and 6 retrospective studies: all the prospective studies and 2 retrospective studies showed a significantly worse PFS for patients with a lower age compared with patients with a higher age at OPG diagnosis. In three prospective trials, age < 1 year emerged as a significant prognostic factor for PFS.[25,26,28] In another prospective trial with similar results, the cut-off point for the variable age was not specified.[12] The 2 retrospective studies with a significant difference in PFS used different cut-off points for age at diagnosis, 15 years[6] or 3.5 years,[14] respectively. Four of the 6 retrospective studies did not detect any difference in PFS for different age. Three of the 4 studies, which evaluated age as a prognostic factor in a univariate analysis showed significant results: 2 studies found a worse PFS for younger children (<1 year[21] or <3 year[23]). In contrast to all the above reported data, one study showed a worse PFS for older children (>5 years[13]). The NF-1 status was evaluated in a multivariate analysis in 3 prospective and 6 retrospective studies. One prospective study[25] and 2 retrospective studies[14,7] found a better PFS for children with OPG affected by NF-1. The other 6 studies, instead, did not find any significant difference between children with and without NF-1. One of the 5 studies which evaluated NF-1 as a prognostic factor in a univariate analysis, and 4 studies based on a χ^2 test found a lower risk of progression for NF-1 patients, in terms of PFS,[11] time-to-progression[8] or progression rate.[9,14,18] Tumour site (along the optic pathway, according to Dodge classification[25]) was evaluated by multivariate analysis in 8 articles. Two studies showed a difference in outcome and found, respectively, that: Dodge I OPG (confined to the optic nerve/s) has a slightly better PFS than chiasmatic (Dodge II) or chiasmatic/hypothalamic glioma (Dodge III)[6] and that Dodge I–II has a better visual outcome than Dodge III.[20] Six studies, instead, showed no significant results by multivariate analysis, for different tumour locations. Two studies documented a significant association between Dodge III and initial progression[25] or between Dodge-II and unfavourable visual outcome,[15] both tested with a χ^2 test.

Regarding the other significant prognostic factors, 1 prospective study[26] found, by multivariate analysis, that children with non-pilocytic astrocytoma of the optic pathways have a higher risk of progression than those with a pilocytic astrocytoma (PA) and 1 retrospective study[27] showed that a histological variant, called pilomyxoid monomorphous astrocytoma (PMA) has a shorter PFS time than PA, at univariate analysis. Furthermore, response to chemotherapy after the first cycle was evaluated in 1 prospective study with multivariate analysis,[25] showing that 'no response' was an independent prognostic factor for a worse PFS. Presence of hydrocephalus at diagnosis[10] and absence of Unidentified Bright Objects (UBOs) lesions in NF-1 children,[24] were both associated with worse PFS, in 1 study with multivariate analysis, respectively.

3.4. *Validity of selected articles*

Data on the external and internal validity of selected articles are described in Table 4. The original study group was assessed as 'well-defined' in all but 5 articles,[14,16,17,19,20] which did not mention age at diagnosis, tumour site or type of intervention. In 8 articles the authors did not define clearly how the population was retrieved,[6,10,11,13,16,17,21,27] so it was not possible to determine if it was a representative sample of the original population. One article retrieved patients based on their prognosis,[14] possibly leading to selection bias, while in another one

less than 90% of eligible patients were included.[28] An adequate follow-up length was assessed in 14 articles and a complete follow-up in all but 6 articles.[12–14,18,23,26] Regarding outcome, 8 studies did not clearly define progression and 3 defined it without modern neuro-radiological techniques (as CT or MRI). All but 2 studies[20,25] did not mention whether the outcome assessment was blind for prognostic factors. A risk estimate was reported in 6 articles as RR[10,12,25] or HR[14,26,28] and 11 articles[6,7,10,12,14,17,20,24–26,28] assessed the influence of other known prognostic factors and adjusted results for possible confounding factors in a multivariate analysis.

4. Discussion

This is the first evidence-based systematic review on childhood OPG: it critically summarises several years of published studies. In this study the best existing evidence supporting the prognostic value of some patient's and tumour characteristics on OPG progression were evaluated. Although several prognostic factors have been investigated and proposed, only a few are supported by solid scientific evidence. Age less than 1 year emerged as the most relevant and scientifically documented prognostic factor for PFS in childhood OPG, with children younger than 1 year having a higher risk for tumour progression than the older ones. Absence of NF-1 status, posterior tumour extension along the optic pathway and the recently investigated new histological features (PMA) also seem to have some prognostic relevance, but no solid scientific evidence supports this statement.

A possible limitation of this systematic review is that only the reported data regarding prognostic analysis and risk estimate were evaluated, without requesting additional informa-

Table 3b – Univariate analysis and χ^2 test prognostic factors results

Author / year	Type of analysis	Type of outcome	Prognostic factors (variables) and risk estimate (*P* value)
Erkal 1997[11]	Univariate log-rank analysis	10 years PFS	• NF-1 (+ versus –): nm* (**P = 0.01**)[a] • Tumour site: (D-I/II versus D-III): nm* (*P* = 0.71)
Packer 1997[13]	Univariate log-rank analysis	3 years PFS	• Age at treatment (<5 years versus >5 years): 74% versus 39% (**P < 0.01**) • NF-1 (+ versus –): 79% versus 65% (*P* = not significant) • Histology (PA versus fibrillary astrocytoma) = 77% versus 63% (*P* = not significant)
Massimino 2002[21]	Univariate log-rank analysis	3- years PFS	• Age at treatment (<1 years versus >1 years): 33% versus 87% (**P = 0.02**); age (<5 years versus >5 years) = 66% versus 100% (*P* = not significant) • NF-1 (+ versus –): 100% versus 73% (*P* = not significant)
Gururangan 2002[22]	Univariate log-rank analysis	3 years PFS	• Age at treatment (>5 years versus <5 years): nm* (*P* = 0.42) • NF-1 (+ versus –): 72% versus 62% (*P* = 0.39)
Khafaga 2003[23]	Univariate log-rank analysis	10 years PFS	• Age at diagnosis (>3 years versus <3 years): 48% versus 75% (**P = 0.01**) • NF-1 (+ versus –): nm* (*P* = 0.26) • Tumour site (D-I/II versus D-III): = 72% versus 58% (*P* = 0.58)
Komotar 2004[27]	Univariate analysis	PFS-time	• Histology (PA versus PMA): 25 months versus 163 months (**P < 0.01**)
Deliganis 1996[8]	χ^2test	Mean time to progression	• NF-1 (+ versus –): 8.37 years versus 2.39 years (**P < 0.05**)
Janss 1996[9]	χ^2test	Progression rate	• NF-1 (+ versus –): 2/ 19 versus 21/29 (**P = 0.0028**)
Shröder 1999[15]	χ^2test	Unfavorable visual outcome	• Mean age at diagnosis (5.8 years versus 3.2 years): 11/25 versus 14/25 (**P < 0.05**) • Tumour site (D-I versus D-II): 3/11 versus 11/14 (**P < 0.05**)
Grill 2000[16]	χ^2test	Progression rate	• NF-1 (+ versus –): 12/20 versus 12/12 (**P = 0.04**)
Kornreich 2001[18]	χ^2test	MRI Tumour enlargement rate	• NF-1 (+ versus –): = 15% versus 37% (**P < 0.001**)
Gayre 2001[19]	χ^2test	Changes in visual acuity (LogMAR)	• NF-1 (+ versus –): = 0.04+/−0.12 versus 0.05+/−0.28 (*P* = 0.4)
Laithier 2003[25]	χ^2test	Initial progression rate	• D-I and D-II versus D-III = nm* (**P = 0.0467**)

CI, 95% confidence interval; D–, Dodge's tumour site classification; Gy, Grey RT dose; HR, hazard ratio; LogMAR, minimum angle resolution; MRI, magnetic resonance images; NF-1, neurofibromatosis type 1; nm, not mentioned; ns, not significant; PA, pilocytic astrocytoma; PFS, progression-free survival; PMA, pilomixoyd monomorphous astrocytoma; RR, relative risk; RT, radiotherapy.

a In bold significant results.

* First term as the favourable prognostic variable.

Table 4 – Validity of the selected articles

Author/year	Study group		Follow-up		Outcome		Prognostic analysis	
	Well-defined	Representative	Long	Complete	Well-defined	Blind	Risk	Adjustment
Kovalic 1990[6]	+	nm	+	+	nm	nm	nm	+
Jenkin 1993[7]	+	+	+	+	nm	nm	nm	+
Deliganis 1996[8]	+	+	+	+	+	nm	nm	–
Janss 1996[9]	+	+	+	+	+	nm	nm	–
Regueiro 1996[10]	+	nm	+	+	+	nm	+	+
Erkal 1997[11]	+	nm	+	+	nm	nm	nm	–
Packer 1997[12]	+	+	–	nm	+	nm	nm	–
Prados 1997[13]	+	nm	–	nm	+	nm	+	+
Chan 1998[14]	nm	–	unclear	nm	nm	nm	+	+
Shroder 1999[15]	+	+	+	+	nm	nm	nm	–
Grill 2000[16]	nm	nm	+	+	+	nm	nm	–
Grabenbauer 2000[17]	nm	nm	+	+	+	nm	–	+
Kornreich 2001[18]	+	+	–	–	+	nm	nm	–
Gayre 2001[19]	nm	+	+	+	+	nm	nm	–
Balcer 2001[20]	nm	+	–	+	+	+	nm	+
Massimino 2002[21]	+	nm	–	+	nm	nm	nm	–
Gururangan 2002[22]	+	+	–	+	+	nm	nm	–
Khafaga 2003[23]	+	+	+	–	nm	nm	nm	–
Fouladi 2003[24]	+	+	+	+	nm	nm	–	+
Laithier 2003[25]	+	+	+	+	+	+	+	+
Gnekow 2004[26]	+	+	–	+	+	–	+	+
Komotar 2004[27]	+	nm	unclear	–	+	unclear	nm	–
Perilongo 2006 (in press)[28]	+	–	+	+	+	–	+	+

+, validity criteria met; –, validity criteria not met; nm, not mentioned.

tion from the authors. Furthermore, the fact that retrospective studies and series including adult patients were included may have lead to selection and/or publication bias. Finally, critical data may have been missed because series from languages other than the ones selected were excluded.

Studies with different internal and external validity were included in this systematic review. Lack of information about items of internal validity, such as representative study group, complete follow-up, blind outcome assessment and adjustment with multivariate analysis, may have lead to different bias and invalid results. For prognostic studies in particular, it is important to adjust analysis for other possible confounding factors: results from univariate or other statistical comparisons (χ^2 test) that do not take into account possible confounding factors may often lead to an over-estimation of the prognostic influence of a single variable. Similarly, missing information for items of external validity, such as a well-defined study group, adequate follow-up length, well-defined outcome and risk estimate, can lead to difficulties in interpreting and extrapolating results correctly to a different population of OPG.

The prognostic value of age less than 1 year is clearly demonstrated by 3 prospective trials, based on children with progressive OPG, which, from a methodological point of view, must be considered very good and adequate.[25,26,28] In 1 of these articles, no methodological limitations could be found, either in internal or external validity.[25] It is possible that, assuming that most of the pilocytic astrocytomas have a limited time-span for growing, those in the very young still have this aggressive growth potential. Many other articles evaluating age as a prognostic factor, however, report heterogeneous cut-off points, without clear and valid conclusions. Only 1 paper pointed out an opposite finding, meaning a worse PFS in children >5 years; however, there was no adjustment for possible confounding factors in this paper, and the patient group included a relatively large number of patients with fibrillary astrocytoma, a rare and more aggressive histological variant of LGG.

NF-1 status has been found to be a prognostic factor for better PFS by various articles, but most of these had some methodological limitations: only 1 study without any limitation demonstrated a lower risk for progression in children with OPG affected by NF-1, independently from age and tumour site.[25] Most of the prospective trials found, instead, no significant value of NF-1 status. One possible explanation is that most of these trials were based on LGG series, and prevalence of NF-1 is not that common in LGG of sites other than the optic pathway. Based on this evidence, we conclude that NF-1 status may well be of some prognostic value for OPG, with children with NF-1 having a slightly better PFS than the ones without NF-1. The prognostic value of tumour site, according to Dodge's classification, is shown by the results of different articles. Posterior tumours along the optic pathway (Dodge II–III) tend to have a worse PFS or visual outcome, but no consisting evidence supports these results. Non-pilocytic histology or PMA variant may have some prognostic value, but is very uncommon in an OPG series population and is not yet supported by evidence.

This aim of this study was not to review the possible clinical and biological hypotheses underlying the prognostic impacts of the clinical variables indicated above, but to show what level our knowledge of prognostic factors for OPG has reached today,

in order to generate research hypotheses and to define clear criteria for starting treatment in children with OPG. This systematic literature review is provides evidence on which to base further prospective clinical trials on childhood LGG.

Conflict of interest statement

None declared.

Acknowledgement

This study was carried out with partial support from the 'Fondazione città della speranza', Italy. We acknowledge Luca Pagnan for logistic support and Arnold Leenders, of the Academic Medical Center (AMC) Library, University of Amsterdam, for support in the search strategy and paper collection process.

REFERENCES

1. Listernick R, Louis DN, Packer RJ, Gutmann DH. Optic pathway gliomas in children with neurofibromatosis 1: consensus statement from the NF1 Optic Pathway Glioma Task Force. *Ann Neurol* 1997;**41**(2):143–9.
2. Parsa CF, Hoyt CS, Lesser RL, et al. Spontaneous regression of optic gliomas: thirteen cases documented by serial neuroimaging. *Arch Ophthalmol* 2001;**119**(4):516–29.
3. Laupacis A, Wells G, Richardson WS, et al. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-based medicine working group. *JAMA* 1994;**272**:234–7.
4. Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ* 2001;**323**:224–8.
5. Van der Pal HJ, van Dalen EC, Kremer LCM, Bakker PJ, van Leeuwen FE. Risk of morbidity and mortality from cardiovascular disease following radiotherapy for childhood cancer: a systematic review. *Cancer Treat Rev* 2005;**31**(3):173–85.
6. Kovalic JJ, Grigsby PW, Shepard MJ, Fineberg BB, Thomas PR. Radiation therapy for gliomas of the optic nerve and chiasm. *Int J Radiat Oncol Biol Phys* 1990;**18**(4):927–32.
7. Jenkin D, Angyalfi S, Becker L, et al. Optic glioma in children: surveillance, resection, or irradiation? *Int J Radiat Oncol Biol Phys* 1993;**25**(2):215–25.
8. Deliganis AV, Geyer JR, Berger MS. Prognostic significance of type 1 neurofibromatosis (von Recklinghausen Disease) in childhood optic glioma. *Neurosurgery* 1996;**38**(6):1114–8. discussion 1118–9.
9. Janss AJ, Grundy R, Cnaan A, et al. Optic pathway and hypothalamic/chiasmatic gliomas in children younger than age 5 years with a 6-year follow-up. *Cancer* 1995;**75**(4):1051–9.
10. Regueiro CA, Ruiz MV, Millan I, de la Torre A, Romero J, Aragon G. Prognostic factors and results of radiation therapy in optic pathway tumors. *Tumori* 1996;**82**(4):353–9.
11. Erkal HS, Serin M, Cakmak A. Management of optic pathway and chiasmatic-hypothalamic gliomas in children with radiation therapy. *Radiother Oncol* 1997;**45**(1):11–5.
12. Prados MD, Edwards SBM, Lamborn K, Davisand V, Levin A. Treatment of pediatric low-grade gliomas with nitrosurea-based multiagent chemotherapy regimen. *J Neuro-Oncol* 1997;**32**:235–41.
13. Packer RJ, Ater J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. *J Neurosurg* 1997;**86**:747–54.
14. Chan MY, Foong AP, Heisey DM, Harkness W, Hayward R, Michalski A. Potential prognostic factors of relapse-free survival in childhood optic pathway glioma: a multivariate analysis. *Pediatr Neurosurg* 1998;**29**(1):23–8.
15. Schroder S, Baumann-Schroder U, Hazim W, Haase W, Mautner VF. Long-term outcome of gliomas of the visual pathway in type 1 neurofibromatosis. *Klin Monatsbl Augenheilkd* 1999;**215**(6):349–54.
16. Grill J, Laithier V, Rodriguez D, Raquin MA, Pierre-Kahn A, Kalifa C. When do children with optic pathway tumours need treatment? An oncological perspective in 106 patients treated in a single centre. *Eur J Pediatr* 2000;**159**(9):692–6.
17. Grabenbauer GG, Schuchardt U, Buchfelder M, et al. Radiation therapy of optico-hypothalamic gliomas (OHG)-radiographic response,vision and late toxicity. *Radiother Oncol* 2000;**54**(3):239–45.
18. Kornreich L, Blaser S, Schwarz M, et al. Optic pathway glioma: correlation of imaging findings with the presence of neurofibromatosis. *AJNR Am J Neuroradiol* 2001;**22**(10):1963–9.
19. Gayre GS, Scott IU, Feuer W, Saunders TG, Siatkowski RM. Long-term visual outcome in patients with anterior visual pathway gliomas. *J Neuroophthalmol* 2001;**21**(1):1–7.
20. Balcer LJ, Liu GT, Heller G, et al. Visual loss in children with neurofibromatosis type 1 and optic pathway gliomas relation to tumor location by magnetic resonance imaging. *Am J Ophthalmol* 2001;**131**(4):442–5.
21. Massimino M, Spreafico F, Cefalo G, et al. High response rate to cisplatin/etoposide regimen in childhood low-grade glioma. *J Clin Oncol* 2002;**20**(20):4209–16.
22. Gururangan S, Cavazos C, Ashley D, et al. Phase II study of Carboplatin in children with progressive low-grade gliomas. *J Clin Oncol* 2002;**13**(1):2951–8.
23. Khafaga Y, Hassounah M, Kandil A, et al. Optic gliomas: a retrospective analysis of 50 cases. *Int J Radiat Oncol Biol Phys* 2003;**56**(3):807–12.
24. Fouladi M, Wallace D, Langston JW, et al. Survival and functional outcome of children with hypothalamic/chiasmatic tumors. *Cancer* 2003;**97**:1084–92.
25. Laithier V, Grill J, Le Deley MC, et al. Progression-free survival in children with optic pathway tumors: dependence on age and the quality of the response to chemotherapy-results of the first French prospective study for the French Society of Pediatric Oncology. *J Clin Oncol* 2003;**21**(24):4572–8.
26. Gnekow AK, Kortmann RD, Pietsch T, Emser A. Low grade chiasmatic-hypothalamic glioma-carboplatin and vincristin chemotherapy effectively defers radiotherapy within a comprehensive treatment strategy – report from the multicenter treatment study for children and adolescents with a low grade glioma – HIT-LGG 1996 – of the Society of Pediatric Oncology and Hematology (GPOH). *Klin Padiatr* 2004;**216**(6):331–42.
27. Komotar RJ, Burger PC, Carson BS, et al. Pilocytic and Pilomyxoid Hypothalamic/Chiasmatic Astrocytomas. *J Neurosurg* 2004;**72**(54):72–80.
28. Perilongo G, Gnekow A, Kortmann R, et al. Treatment results of the first cooperative chemotherapy trial run by the International Research Consortium on Childhood Low Grade Glioma – LGG93 – a study of the Brain Tumor Sub-Committee of the International Society of Pediatric Oncology (SIOP). *Eur J Cancer* 2006, in press.