Neuro-Oncology

Loss of heterozygosity 1p/19q and survival in glioma: a meta-analysis

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Background. Glioma is rarely curable, and factors that influence the prognosis of glioma patients are not fully understood. Loss of heterozygosity (LOH) of 1p/19q has long been known to be a typical molecular signature of oligodendroglial neoplasms. However, whether LOH of 1p/19q is associated with survival in gliomas remains controversial. Here our goal was to evaluate the association between LOH of 1p/19q and progression-free survival (PFS) and overall survival (OS) by conducting a meta-analysis among glioma cases.

Methods. The PubMed and Embase databases were searched from the earliest records to May 2013 to identify studies that met prestated inclusion criteria. Reference lists of retrieved articles were also reviewed. Three authors independently extracted information needed for further analysis. Either a fixed- or a random-effects model was used to calculate the overall combined hazard ratio (HR) estimates.

Results. Twenty-eight eligible studies involving 3 408 cases were included in the meta-analysis. Compared with the chromosomal intact group, codeletion of 1p and 19q was associated with a better PFS (HR = 0.63; 95% CI, 0.52–0.76) and OS (HR = 0.43; 95% CI, 0.35–0.53). Subgroup analyses showed this association to be independent of detection methods and the grades and subtypes of gliomas. Furthermore, isodeletion of chromosome 1p predicted a similar favorable disease outcome (PFS: HR = 0.68; 95% CI, 0.47–0.97) (OS: HR = 0.51; 95% CI, 0.35–0.75), especially in low-grade gliomas, whereas isodeletion of 19q only indicated longer PFS (HR = 0.70; 95% CI, 0.56–0.87).

Conclusion. Codeletion of 1p and 19q is associated with better survival rates in glioma. Isodeletion of 1p predicts similar outcomes but to a lesser extent, whereas the effects of isodeletion of 19q remained only marginal.

Keywords: 1p, 19q, glioma, meta-analysis, survival.

As the most frequent primary brain tumor, gliomas account for approximately 30% of all brain and central nervous system tumors and 80% of all malignant brain tumors.[1] Based on their histological appearance, gliomas can be divided into 2 major subtypes according to the 2007 WHO classification:[2] One is astrocytic tumors including pilocytic astrocytomas (PA), astrocytomas, and glioblastomas (GBM); the other is oligodendroglial tumors including pure oligodendrogliomas and mixed oligoastrocytic tumors. Tumors can be further divided into grades I (PA), II (low grade), III (anaplastic), and IV (GBM) depending on the presence of anaplastic features.[2]

Factors that influence the prognosis for glioma patients are not completely understood. The combination of surgery, radiotherapy, and chemotherapy remains the standard treatment in most cases; however, not all patients derive clinical benefit from it. It has been recognized that acquired molecular abnormalities have been associated with histological subtype and grade.[1,3] Specific molecular abnormalities and/or genetic mutation patterns are believed to

be associated with the prognosis of gliomas and can differentiate not only among histological subtypes but also between low-grade (grades I and II) and high-grade (grades III and IV) tumors. Combined loss of genetic materials on chromosomal arms 1p and 19q from an unbalanced translocation can lead to the loss of 1 hybrid chromosome and thereby loss of heterozygosity (LOH).[4] LOH of 1p/19q has long been known to be a typical molecular signature of oligodendroglial neoplasms;[5] now, accumulating data suggest that LOH of 1p/19q is present in about 80% of low-grade oligodendrogliomas, 60% of anaplastic oligodendrogliomas (AO), 30%–50% of oligoastrocytomas, 30% of anaplastic oligoastrocytomas, and 10% of diffuse astrocytic gliomas including GBM.[6] In 1998, it was first reported that LOH of 1p/19q could predict better response to chemotherapy and longer survival in AO patients.[7] Soon thereafter, studies including prospective randomized phase III trials demonstrated that a LOH of 1p/19q status was associated with good outcome and might consequently play an important role in the treatment.[8,9] However, the magnitudes

of the association varied between studies: some studies[10,11] even failed to show such a positive association.

An improved understanding of this issue could have important public health and clinical implications considering that gliomas are still rarely curable. With recently accumulating evidence, our goal therefore, was to evaluate the association between LOH of 1p/19q and progression-free survival (PFS) and overall survival (OS) by conducting a meta-analysis among patients with different grades and subtypes of gliomas. Additionally, the relationships between isodeletion of chromosomal arms 1p or 19q and clinic outcomes were examined.

Method

Search Strategy and Selection of Studies

The current meta-analysis was carried out in accordance with the PRISMA statement for reporting systematic reviews and meta-analyses.[12] PubMed and Embase were searched for studies evaluating the deletions involving chromosomal arms 1p/19q and survival in brain tumors from the earliest records to May 2013. The following search terms were used: (i) glioma, brain tumor, oligodendroglioma, oligodendroglial tumor, glioblastoma, astrocytoma, astrocytic tumor, oligoastrocytoma, oligodendroglial neoplasm; and (ii) chromosomal arms deletion, codeletion, loss of heterozygosity, 1p, 19q. Only one restriction was imposed, that for clinical studies. In addition, the reference lists of retrieved papers were reviewed.

The search results were first screened for titles and/or abstracts. A second screening was based on full-text review. Studies were considered eligible if they met the following criteria: (i) the exposures of interest were glioma and chromosomal arms 1p and 19q; (ii) the outcomes of interests were progression-free survival and overall survival; (iii) hazard ratio (HR) and the corresponding 95% confidence interval (CI) (or data sufficient to calculate them) were reported; and (iv) exclusion of letters to the editor, reviews, and articles published in non-English language books or papers.

Data Collection and Extraction

Three authors (J. Zhao, W. Ma and H. Zhao) independently extracted information using predefined data abstraction forms. The following details were extracted: first author's full name, year of publication, country of origin, tumor subtype, tumor grade, median age at the time of diagnosis, duration of follow-up, method to detect 1p/19q, total number of cases, number of LOH of 1p/19q cases and controls, subtype of 1p/19q experiment vs control, number of 1p loss cases and controls, number of 19q loss cases and controls, and assessments of outcomes (HR and the corresponding 95% CI of PFS and/or OS. When the statistical variables were not given explicitly in an article, they were estimated from available data using methods reported by Tierney et al.[13] If one study reported both the results of univariate and multivariate analysis, the latter was selected.

The key exposure variable was the codeletion of 1p/19q at baseline, but patients with 1p/19q isodeletion and codeletion served as the experimental group in 7 studies.,[14–20] In addition, patients with intact 1p/19q were treated as reference groups in most studies, while in 2 studies,[21,22] those with isodeletion and intact 1p/19q served as controls. The rest of the papers assessed only the outcomes of both codeletion and intact 1p/19q. The studies selected for specific meta-analysis were indicated in the context. We required a minimum of 3 studies to carry out pooled analyses.

Statistical Analysis

Homogeneity of HRs across the studies was tested by Q statistic (significance level at $P < .05$). The I^2 statistic, a quantitative measure of inconsistency across studies,[23] was also calculated. The combined risk estimates were computed by fixed-effects models if the I^2 statistic was <50%; otherwise, the random-effects models were used.[24]

Because characteristics of populations, ascertainment of different glioma subtypes, and adjustments for confounding factors were not consistent between studies, we further conducted a sensitivity analysis to explore possible explanations for heterogeneity and to examine the influence of various exclusion criteria on the overall risk estimate. We also investigated the influence of a single study on the outcome estimate by omitting one study in each turn.

Potential publication bias was assessed by visual inspection of the Begg's funnel plots. We also performed the Begg rank correlation test at the $P < .10$ level of significance.[25] All analyses were performed using STATA version 12.0 (StataCorp LP). A $P < .05$ was considered statistically significant, except where otherwise specified.

Result

Literature Search

Of 698 titles initially retrieved, 617 were excluded because they did not meet the inclusion criteria. Of the remaining 81 studies, all were found in full text and were evaluated by 3 independent investigators; 53 papers were excluded because of duplication, nonstandard outcome measure, and noncoherence with inclusion criteria. A total of 28 studies[8–11,14–22,26–40] were ultimately included in this meta-analysis. A flow chart showing the study selection is presented in Fig. 1.

Study Characteristics

The characteristics of the selected 28 studies are presented in Table 1. These papers were published between 2004 and 2013. Six studies were conducted in the US and Canada, 16 in Europe, 3 in Asia, 2 in Australia, and 1 in multiple countries. The mean length of follow-up ranged from 14 to 107 months. A total of 3 408 cases were included in the current meta-analysis, of which 898 were low-grade glioma, 1 725 were high-grade glioma, and the remaining 785 were not specified. When these 3 408 cases were classified by their histological feature, 791 were astrocytic tumors, 1 451 were oligodendroglial tumors, and the tumor subtypes of the remaining 1166 cases were not indicated. Of the total 28 studies, 12 studies detected the chromosomal arm 1p/19q status by PCR or RT-PCR, 11 studies used fluorescent in situ hybridization (FISH), and the remaining 5 studies detected 1p/19q by
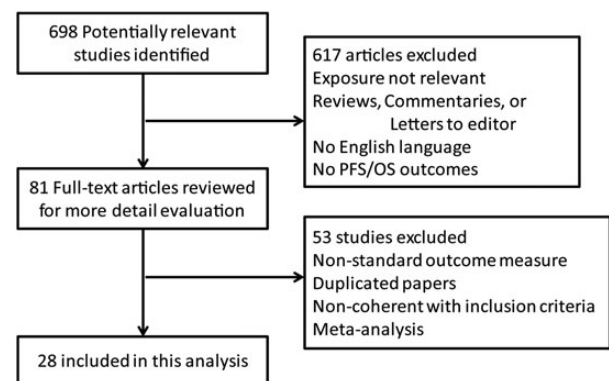

Fig. 1. Flow chart of study selection. Flow chart shows literature search for studies of loss of 1p/19q heterozygosity in relation to survivals in glioma.

Table 1. Main characteristics of all studies included in current meta-analysis

Author	Year	Country	Tumor Subtype[a]	Tumor Grade	Median Age (range)	Median Follow-up (months)	Method to Detect 1p/19q	No. of Patients (LOH 1p/19q: control)	1p/19q Experimental vs Control Subtype[b]
Fallon	2004	US and Canada	2	High	39.2 (20–71)	106.8	FISH	76 (54:22)	2
Walker	2005	UK	2	Mixed	40 (21–73)	39.6	PCR	100 (46:54)	1
Kujas	2005	France	3	Low	39 (17–66)	63.3	FISH	127 (49:68)	1
Dehais	2006	France	1	High	45.5 (20–83)	57.3	PCR	143 (27:116)	1
Brandes	2006	Italy	2	High	47.8 (18–70)	NR	FISH	67(32:35)	2
Miller	2006	US	3	High	52.4 (21–90)	16.8	FISH	389(212:177)	1
Homma	2006	Switzerland	1	Mixed	55.4	NR	PCR	209(6:203)	2
Mariani	2006	Switzerland	3	Low	38.3 (20–76)	71	PCR	66 (17:49)	1
Kaloshi	2007	France	1	Low	44 (24–72)	30.4	PCR	86 (36:50)	3
Iwamoto	2008	US	3	Low; high	38.9	56.1	PCR	111 (39:72)	1
Idbaih	2008	France	2	High	50.3 (23–84)	NR	PCR	52 (15:37)	1
Wick	2009	German	3	High	43.0 (20–77)	54(max)	Other	181 (74:107)	1
Weller	2009	German	1	Mixed	61.5 (19–87)	29.4	PCR	281 (24:257)	1
Mikkelsen	2009	US	2	High	45.5 (18–81)	32	Other	48 (36:12)	2
Kesari	2009	US	2	Low	43 (20–68)	39.4	FISH	28 (18:10)	1
Kuo	2009	Taiwan	2	Mixed	38 (4–82)	83	PCR	49 (34:15)	1
Gravendeel	2009	Netherlands	3	Mixed	50.2 (12–81)	NR	FISH	NR	1
Gan	2010	Australia	2	Low	43 (17–71)	34	PCR	37 (18:19)	1
Ji	2010	China	2	Low; high	43.1 (10–76)	NR	PCR	131 (100:31)	2
Kim	2010	Switzerland, German, Japan	3	Low	39 (> 20)	NR	PCR	268 (112:156)	2
Scheie	2011	Norway	2	Mixed	43 (19–72)	50	FISH	95 (52:43)	2
Parkinson	2011	Australia	2	Mixed	52.4 (25–80)	NR	FISH	51 (26:25)	1
Grauer	2011	German	3	High	40.5 (18–66)	52.9	Other	24 (21:3)	1
Taal	2011	Netherlands	1	Low	38 (25–59)	14	FISH	NR	1
Hartmann	2011	German	1,2	Low	39	64.8	FISH	133 (51:82)	1
Li	2012	China	2	High	43 (16–71)	38.2	Other	77 (28:49)	1
Cairncross	2013	US and Canada	2	High	43 (18–76)	NR	FISH	263 (126:137)	3
Erdem-Eraslan	2013	Europe	2	High	49.5 (19–69)	NR	Other	316 (80:236)	1

[a]Tumor subtype. Type 1: astrocytic tumors including pilocytic astrocytomas, astrocytomas, and glioblastomas; type 2: oligodendroglial tumors including pure oligodendroglial tumors and mixed oligoastrocytic tumors; type 3: mixed subtype.
[b]1p/19q experimenal vs control subtype. Type 1: 1p/19q codeletion vs intact 1p/19q; type 2: 1p/19q isodeletion and codeletion vs intact 1p/19q; type 3: 1p/19q codeletion vs 1p/19q isodeletion and intact 1p/19q.
Abbreviations: FISH, fluorescent in situ hybridization; LOH, loss of heterozygosity; NR, not reported.

other methods such as denaturing high-performance liquid chromatography, array comparative genomic hybridization, and multiplex ligation–dependent probe amplification. As a result, 1 333 cases showed LOH of 1p/19q, of which 765 demonstrated codeletion of 1p and 19q.

LOH of 1p/19q and PFS

Since the key exposure variable was the codeletion of chromosomal arms 1p and 19q, 11 studies that assessed PFS for both codeletion and intact 1p/19q were strictly analyzed first (Fig. 2a). The absence of both 1p and 19q was significantly associated with better PFS (HR = 0.63; 95% CI, 0.52–0.76; $n = 11$; $P < .001$). Further subgroup analysis showed that codeletion of 1p/19q

indicated better PFS in both low-grade tumors (HR = 0.65; 95% CI, 0.50–0.85; $n = 5$; $P < .001$) and high-grade gliomas (HR = 0.62; 95% CI, 0.46–0.84; $n = 4$; $P < .001$). In current meta-analysis, heterogeneity, the variation in study outcomes between studies was measured by P value and I^2, the percentage of variation across studies that is due to heterogeneity rather than random chance. No heterogeneities were observed between different subgroups ($P = .91$) and individual studies ($I^2 = 10.0\%$; $P = .35$). Similar analysis suggested that codeletion of 1p/19q indicated good PFS in oligodendroglial tumors (HR = 0.65; 95% CI, 0.48–0.87; $n = 6$, $P < .01$) (Table 2). Patients with 1p/19q isodeletion and codeletion served as the experimental group in 4 other studies. Analysis on all these 15 papers showed that LOH of 1p/19q was associated with better PFS (HR = 0.56; 95% CI, 0.47–0.67;
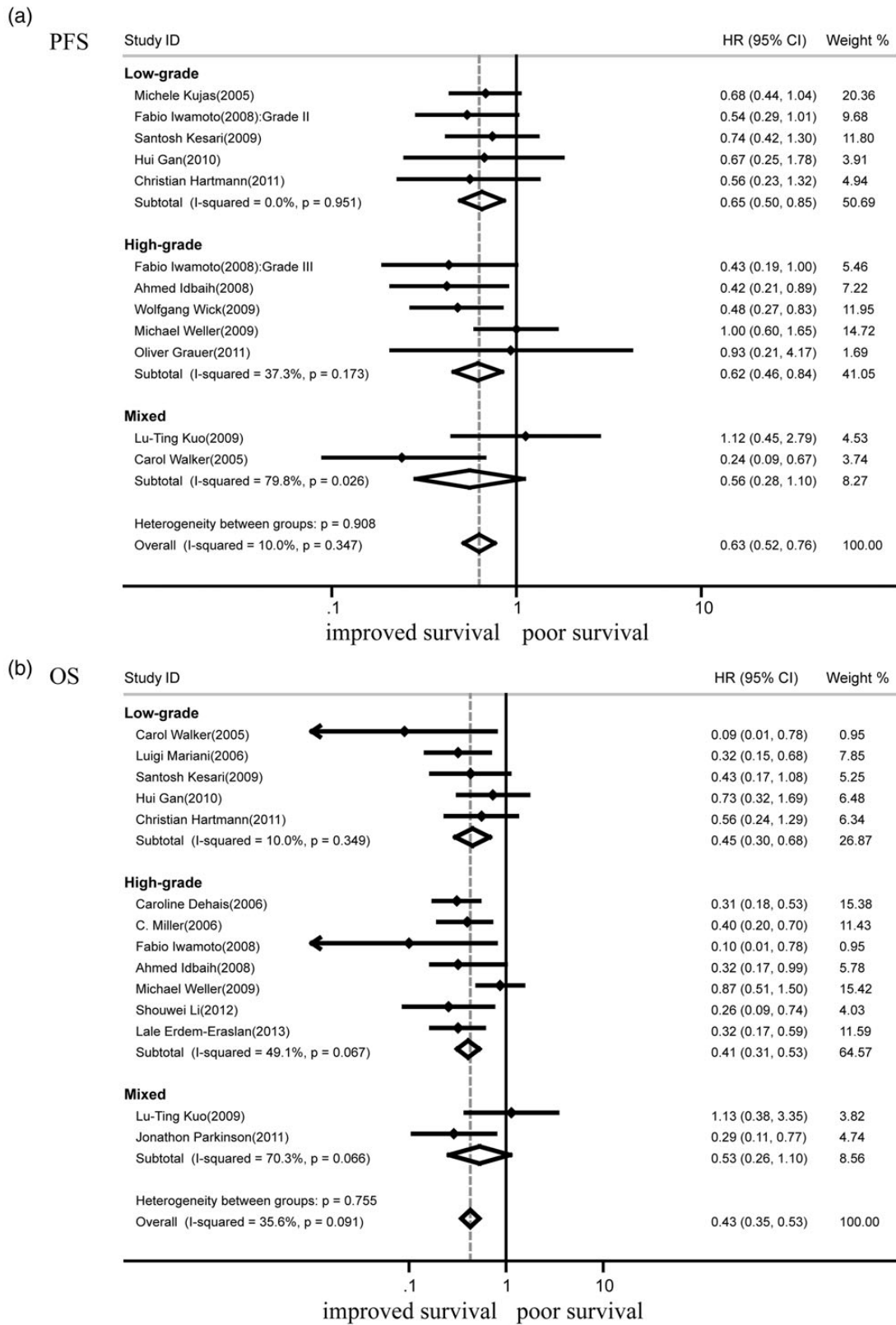
(a)

PFS

Study ID	HR (95% CI)	Weight %
Low-grade		
Michele Kujas(2005)	0.68 (0.44, 1.04)	20.36
Fabio Iwamoto(2008):Grade II	0.54 (0.29, 1.01)	9.68
Santosh Kesari(2009)	0.74 (0.42, 1.30)	11.80
Hui Gan(2010)	0.67 (0.25, 1.78)	3.91
Christian Hartmann(2011)	0.56 (0.23, 1.32)	4.94
Subtotal (I-squared = 0.0%, p = 0.951)	0.65 (0.50, 0.85)	50.69
High-grade		
Fabio Iwamoto(2008):Grade III	0.43 (0.19, 1.00)	5.46
Ahmed Idbaih(2008)	0.42 (0.21, 0.89)	7.22
Wolfgang Wick(2009)	0.48 (0.27, 0.83)	11.95
Michael Weller(2009)	1.00 (0.60, 1.65)	14.72
Oliver Grauer(2011)	0.93 (0.21, 4.17)	1.69
Subtotal (I-squared = 37.3%, p = 0.173)	0.62 (0.46, 0.84)	41.05
Mixed		
Lu-Ting Kuo(2009)	1.12 (0.45, 2.79)	4.53
Carol Walker(2005)	0.24 (0.09, 0.67)	3.74
Subtotal (I-squared = 79.8%, p = 0.026)	0.56 (0.28, 1.10)	8.27
Heterogeneity between groups: p = 0.908		
Overall (I-squared = 10.0%, p = 0.347)	0.63 (0.52, 0.76)	100.00

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improved survival　　poor survival

(b) OS

Study ID	HR (95% CI)	Weight %
Low-grade		
Carol Walker(2005)	0.09 (0.01, 0.78)	0.95
Luigi Mariani(2006)	0.32 (0.15, 0.68)	7.85
Santosh Kesari(2009)	0.43 (0.17, 1.08)	5.25
Hui Gan(2010)	0.73 (0.32, 1.69)	6.48
Christian Hartmann(2011)	0.56 (0.24, 1.29)	6.34
Subtotal (I-squared = 10.0%, p = 0.349)	0.45 (0.30, 0.68)	26.87
High-grade		
Caroline Dehais(2006)	0.31 (0.18, 0.53)	15.38
C. Miller(2006)	0.40 (0.20, 0.70)	11.43
Fabio Iwamoto(2008)	0.10 (0.01, 0.78)	0.95
Ahmed Idbaih(2008)	0.32 (0.17, 0.99)	5.78
Michael Weller(2009)	0.87 (0.51, 1.50)	15.42
Shouwei Li(2012)	0.26 (0.09, 0.74)	4.03
Lale Erdem-Eraslan(2013)	0.32 (0.17, 0.59)	11.59
Subtotal (I-squared = 49.1%, p = 0.067)	0.41 (0.31, 0.53)	64.57
Mixed		
Lu-Ting Kuo(2009)	1.13 (0.38, 3.35)	3.82
Jonathon Parkinson(2011)	0.29 (0.11, 0.77)	4.74
Subtotal (I-squared = 70.3%, p = 0.066)	0.53 (0.26, 1.10)	8.56
Heterogeneity between groups: p = 0.755		
Overall (I-squared = 35.6%, p = 0.091)	0.43 (0.35, 0.53)	100.00

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improved survival　　poor survival

Fig. 2. Forest plots showing hazard ratios of codeletion of 1p/19q for progression-free survival (a) and overall survival (b). Each study is shown by the point estimate of the hazard ratio and 95% confidence intervals (extending lines). The diamonds represent the estimated pooled effect (labeled total).

Table 2. Hazard ratios of different human chromosome 1p/19q heterozygosity vs intact 1p/19q status for progression-free survival and overall survival

Studies	HR (95% CI)
PFS	
Codeletion of 1p/19q in oligodendroglial tumors (16, 22, 25, 26, 28, 32)	0.65 (0.48–0.87)
LOH of 1p/19q in glioma (5–7, 9, 16, 17, 21–26, 28, 30, 32)	0.56 (0.47–0.67)
PCR to detect 1p/19q (16, 21, 22, 24, 26, 28)	0.63 (0.47–0.83)
FISH to detect 1p/19q (17, 25, 32)	0.68 (0.49–0.94)
OS	
Codeletion of 1p/19q in astrocytic tumors (18, 24, 32)	0.52 (0.36–0.75)
Codeletion of 1p/19q in oligodendroglial tumors (16, 22, 25, 26, 28, 29, 32–34)	0.41 (0.30–0.56)
LOH of 1p/19q in gliomas (4–7, 10, 16, 18–22, 24–26, 28, 29, 32, 34)	0.41 (0.34–0.48)
1p deletion in astrocytic tumors (8, 18, 24)	0.65 (0.38–1.12)
19q deletion in astrocytic tumors (8, 18, 24, 31)	0.64 (0.43–0.95)
19q deletion in oligodendroglial tumors (4, 25, 26)	1.12 (0.10–12.09)
PCR to detect 1p/19q (16, 18, 20–22, 24, 26, 28, 33)	0.46 (0.35–0.60)
FISH to detect 1p/19q (19, 25, 29, 32)	0.39 (0.25–0.60)

Abbreviations: FISH, fluorescent in situ hybridization; LOH, loss of heterozygosity

$P < .001$ (Table 2); there was no substantial heterogeneity for the outcome ($I^2 = 27.2\%$, $P = .15$).

LOH of 1p/19q and OS

A total of 14 studies that assessed OS of both codeletion and intact 1p/19q were analyzed (Fig. 2b). The deletion of both 1p and 19q was clearly associated with good OS (HR = 0.43; 95% CI, 0.35–0.53; $n = 14$, $P < .001$). Subsequent subgroup analysis showed that codeletion of 1p/19q also indicated favorable outcomes in both low-grade tumors (HR = 0.45; 95% CI, 0.30–0.68; $n = 5$, $P < .001$) and high-grade gliomas (HR = 0.41; 95% CI, 0.31–0.53; $n = 6$, $P < .001$). No heterogeneities were observed between subgroups ($P = .76$) and all 14 studies ($I^2 = 35.6\%$, $P = .09$). Similar analysis suggested that codeletion of 1p/19q indicated good OS in astrocytic tumors (HR = 0.52; 95% CI, 0.36–0.75; $n = 3$; $P < .001$) and oligodendroglial tumors (HR = 0.41; 95% CI, 0.30–0.56; $n = 9$, $P < .001$) (Table 2). Patients with 1p/19q isodeletion and codeletion served as the experimental group in 5 other studies. Analysis on these 19 papers showed that LOH of 1p/19q was associated with better OS (HR = 0.41; 95% CI, 0.34–0.48; $P < .001$) (Table 2), and there was no substantial heterogeneity for the outcome ($I^2 = 36.3\%$; $P = .06$).

1p Deletion and PFS

Nine studies assessed the outcomes of chromosomal arm 1p deletion. A total of 1 282 cases were included, of which 442 showed 1p loss; the other 840 cases had intact 1p. The absence of 1p was associated with better PFS (HR = 0.68; 95% CI, 0.47–0.97; $n = 5$: $P < .05$) (Fig. 3a). There was heterogeneity between studies in this analysis ($I^2 = 62.4\%$; $P = .02$). Sensitivity analyses were immediately conducted to explore potential sources of heterogeneity in the association between 1p deletion and PFS and to examine the influence of various exclusion criteria on the overall risk estimate. GBM was the most deadly of malignant primary brain tumors. It was reported that median survival with standard-of-care radiation and chemotherapy with temozolomide was about 15 months, and median survival without treatment was 4.5 months.[41] Exclusion of the study that only focused on GBM[10] yielded better results (HR = 0.55; 95% CI, 0.43–0.71; $P < .001$) with no evidence of heterogeneity observed among the remaining studies ($I^2 = 0\%$, $P = .79$). Further subgroup analysis showed that deletion of 1p indicated good PFS in low-grade tumors (HR = 0.51; 95% CI, 0.38–0.69; $n = 3$; $P < .001$) (Fig. 3a). After excluding the GBM study,[10] there were not enough data to conduct meta-analysis in high-grade gliomas, oligodendroglial tumors, and astrocytic tumors.

1p Deletion and OS

A total of 8 studies that assessed OS for deletion and intact 1p were analyzed (Fig. 3b). The absence of 1p was associated with good OS (HR = 0.51; 95% CI, 0.35–0.75; $n = 8$; $P < .001$). Heterogeneity was observed for the outcome ($I^2 = 62.0\%$; $P < .01$). The exclusion of one study focused on GBM[10] hardly changed the overall hazard ratio (HR = 0.47; 95% CI, 0.36–0.60; $n = 7$; $P < .001$) with no substantial heterogeneity ($I^2 = 0\%$; $P = .49$). Subgroup analysis showed that deletion of 1p indicated good OS in low-grade tumors (HR = 0.32; 95% CI,.018–0.56; $n = 3$; $P < .001$). Based on the available data, the associations between 1p loss and OS were inconclusive in high-grade gliomas (HR = 0.57; 95% CI, 0.27–1.18; $n = 3$; $P > .05$) (Fig. 3b) and astrocytic tumors (HR = 0.65; 95% CI, 0.38–1.12; $n = 3$, $P > .05$) (Table 2).

19q deletion and PFS

Eleven studies assessed the outcomes of chromosomal arm 19q deletion. A total of 1 311 glioma cases were included, of which 387 showed 19q loss, while 924 had intact 19q. The absence of 19q was associated with better PFS (HR = 0.70; 95% CI, 0.56–0.87; $n = 6$, $P < .01$) (Fig. 4a). There was no substantial heterogeneity between studies ($I^2 = 39.1\%$; $P = .13$). Subgroup analysis showed that deletion of 19q indicated good PFS in low-grade tumors (HR = 0.70; 95% CI, 0.51–0.95; $n = 4$; $P < .01$) (Fig. 4a).

19q deletion and OS

A total of 10 studies that assessed OS for deleted and intact 19q were analyzed (Fig. 4b). Based on the available data, no association of 19q loss and OS was evident (HR = 0.66; 95% CI, 0.37–1.19; $n = 10$, $P > .05$). Substantial heterogeneity was observed for the outcome ($I^2 = 81.9\%$; $P < .001$). Sensitivity analyses were conducted to explore potential sources; it turned out that exclusion of any 1 or 2 studies did not change the heterogeneity. Exclusion of all 7 investigations that contained high-grade gliomas showed a better OS (HR = 0.40; 95% CI, 0.25–0.65; $n = 4$; $P < .001$) with no substantial heterogeneity ($I^2 = 0\%$; $P = .45$). Loss of 19q was associated with OS in astrocytic tumors (HR = 0.64; 95% CI,
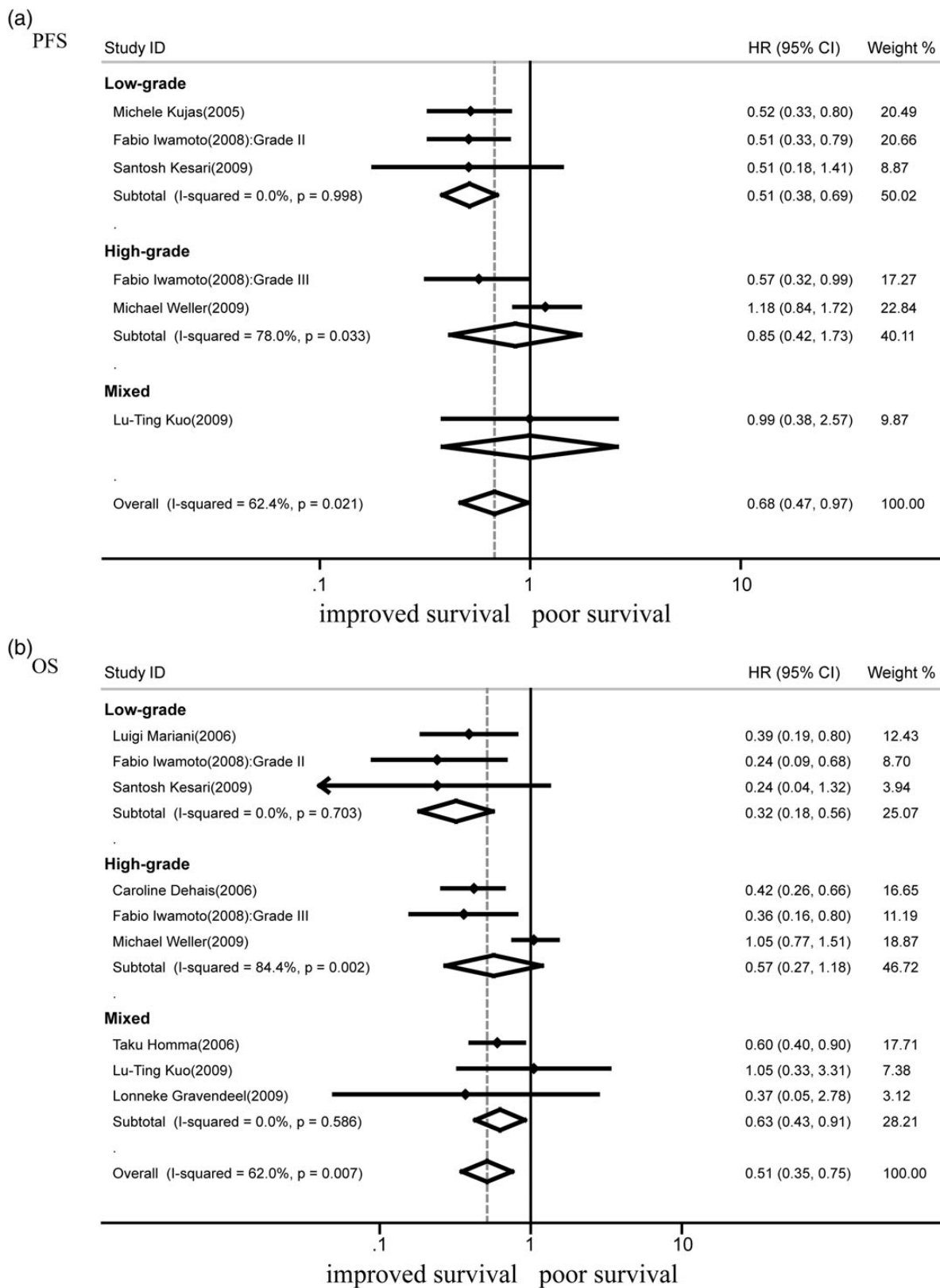
(a)
PFS

(b)
OS

Fig. 3. Forest plots showing hazard ratios of isodeletion of 1p for progression-free survival (a) and overall survival (b).
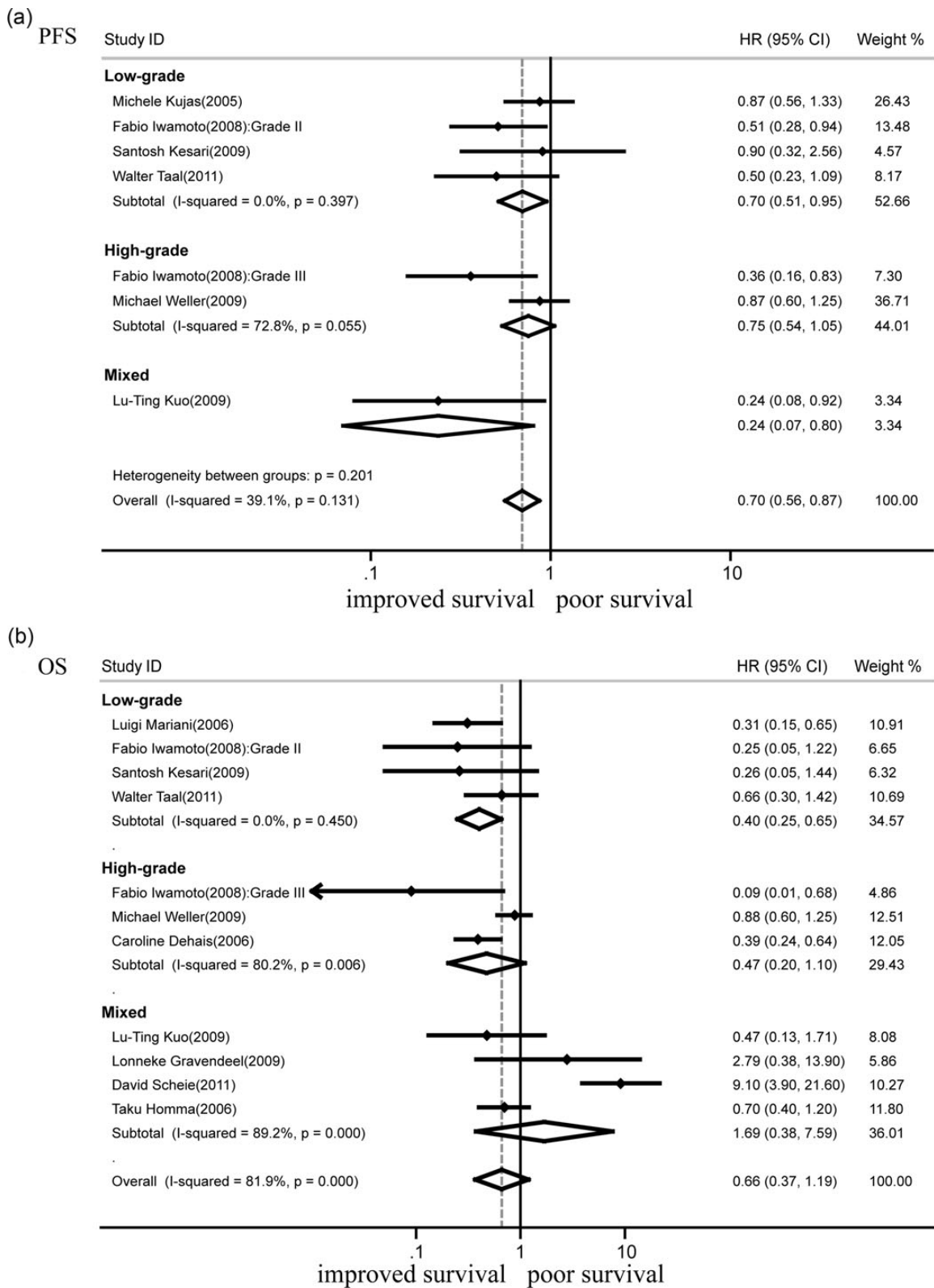
Fig. 4. Forest plots showing hazard ratios of isodeletion of 19q for progression-free survival (a) and overall survival (b).

0.43–0.95; $n = 4$; $P < .05$) but not in oligodendroglial tumors (HR = 1.12; 95% CI, 0.10–12.09; $n = 3$; $P > .05$) (Table 2).

Methods of 1p/19q Detection and Outcome

There was no difference in the hazard ratio for PFS or OS (Table 2) between studies utilizing PCR and those using FISH to assess the status of chromosomal arms 1p and 19q (P values for subgroup differences were .71 and .53, respectively).

Publication Bias

Potential publication bias was assessed by Begg's funnel plots and Begg's rank correlation. Visual inspection of the Begg's funnel plot did not identify substantial asymmetry. The Begg's rank correlation test also indicated no evidence of publication bias among studies of gliomas and LOH of 1p/19q ($P = .92$).

Discussion

In this study, we meta-analyzed the published data about chromosomal arms 1p/19q status in gliomas and their association with survival. Results show that codeletion of 1p and 19q was associated with a more favorable disease outcome and that this association was independent of detection methods, grades, and subtypes of gliomas. Isodeletion of chromosomal arm 1p also predicted longer PFS and OS, especially in low-grade gliomas. The effects of isodeletion of 19q remained only marginal.

LOH of 1p/19q and Survival

Loss of 1p and 19q due to an unbalanced centromeric translocation t (1;19) (q10; p10) were first associated with sensitivity to alkylating agent chemotherapy[7] and later to sensitivity to radiotherapy as well.[42] Here, our results confirmed that codeletion of 1p/19q was associated with favorable clinic outcomes. Further subgroup meta-analysis suggested that codeletion of 1p/19q was an independent predictive biomarker.

Although usually both chromosomes 1p and 19q are lost, isodeletion of 1p or 19q is still very common in gliomas.[43] Unfortunately, most research merely focused on codeletion of 1p/19q rather than single loss of 1p or 19q. Our data demonstrated that single loss of 1p could predict longer survival in the low-grade tumors. High-grade glioma patients, especially GBM patients, could not derive clinical benefit from isodeletion of 1p. There are several reasons to explain the inconsistency. First, it was reported there were 2 types of 1p loss with opposite significance in gliomas.[44] Type II 1p loss, mainly observed in GBM and not associated with 19q loss, had an unfavorable prognostic value. Second, the presence of other prognostically unfavorable genetic alterations (ie, chromosomal arm 9p or 10q loss) could compromise the prognostic utility.[45,46] Third, only GBM-O, one subtype of GBM, contained 1p and/or 19q deletion,[2] but the reported LOH of 1p/19q frequencies varied from 5%[47,48] to about 25%.[49,50] The rare cases of 1p/19q deletion in GBM made it difficult to collect sufficiently powered studies.

Sources of Heterogeneity

No substantial heterogeneity was observed among studies of 1p/19q codeletion status and clinical outcome, even when there were significant differences in characteristics of populations, ascertainment of tumor subtype, and adjustment for confounding factors. As to 19q loss analysis, substantial heterogeneity was observed and no single major source could be detected through the sensitivity analysis, only excluded all the high-grade tumors could change the heterogeneity. Both statistical and clinical heterogeneity could contribute to this result. Clinical heterogeneity may derive from the different patients (with different ages, tumor sizes, ethnicity, physical condition, etc.), diverse types of treatments, various treatment protocols, different doses and types of drugs, and so on. Further multicenter research, using standardized methods, is encouraged.

Assessment of chromosomal arm 1p/19q status is most frequently accomplished by FISH, PCR-based LOH analysis, and multiplex ligation-dependent probe amplification. Of these methods, FISH has proven to be robust, easy to implement, and cost effective.[51] In the current study, we found that there was no observed difference between studies using PCR and those using FISH when assessing the clinical outcome of glioma cases with LOH of 1p/19q. This suggested that chromosomal arm detection methods could not be the source of heterogeneity and that the 1p/19q codeletion pattern would be a powerful prognostic and predictive biomarker in neuro-oncology practice.

Study Strengths and Limitations

Our meta-analyses generated several important implications. First, analyzing LOH for 1p and/or 19q and PFS and OS in gliomas made our results more extensive and valid. Second, the association of 1p/19q codeletion with survival persists and remains statistically significant based on various classification criteria. Third, with the accumulating evidence and enlarged sample size, we have enhanced statistical power to provide more precise and reliable hazard ratio estimates. Fourth, all of the analyses were conducted by random-effects models and fixed-effects models (data not shown). Both models showed similar results, which indicated that the statistical results were robust.

Despite its advantages, our meta-analysis had some limitations. First, publication bias was a major concern that may cause bias. In this research, Begg's funnel plot did not show any evidence of publication bias. Nevertheless, we still need to consider the fact that studies with positive data are more easily accepted. First, the languages of the published studies included in this meta-analysis were restricted to English, and other potentially eligible studies that met our inclusion criteria could not be included. Second, the number of studies concerning some histological subtypes (such as pilocytic astrocytomas and glioblastomas) were too small to perform a pooled analysis. Third, most of the glioma patients were treated with different combination therapies. Some patients were treated with neurosurgery alone. Fourth, evaluation standards and cut-off values for LOH chromosomal arm 1p/19q may also be different in various studies.

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