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Radiological Recurrence Patterns after Bevacizumab Treatment of Recurrent High-Grade Glioma: A Systematic Review and Meta-Analysis

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Objective: To categorize the radiological patterns of recurrence after bevacizumab treatment and to derive the pooled proportions of patients with recurrent malignant glioma showing the different radiological patterns.

Materials and Methods: A systematic literature search in the Ovid-MEDLINE and EMBASE databases was performed to identify studies reporting radiological recurrence patterns in patients with recurrent malignant glioma after bevacizumab treatment failure until April 10, 2019. The pooled proportions according to radiological recurrence patterns (geographically local versus non-local recurrence) and predominant tumor portions (enhancing tumor versus non-enhancing tumor) after bevacizumab treatment were calculated. Subgroup and meta-regression analyses were also performed.

Results: The systematic review and meta-analysis included 17 articles. The pooled proportions were 38.3% (95% confidence interval [CI], 30.6–46.1%) for a geographical radiologic pattern of non-local recurrence and 34.2% (95% CI, 27.3–41.5%) for a non-enhancing tumor-predominant recurrence pattern. In the subgroup analysis, the pooled proportion of non-local recurrence in the patients treated with bevacizumab only was slightly higher than that in patients treated with the combination with cytotoxic chemotherapy (34.9% [95% CI, 22.8–49.4%] versus 22.5% [95% CI, 9.5–44.6%]).

Conclusion: A substantial proportion of high-grade glioma patients show non-local or non-enhancing radiologic patterns of recurrence after bevacizumab treatment, which may provide insight into surrogate endpoints for treatment failure in clinical trials of recurrent high-grade glioma.

Keywords: *Bevacizumab; Glioblastoma; Magnetic resonance imaging; Radiology*

INTRODUCTION

Among various options, bevacizumab is available for the treatment of recurrent glioblastoma. It is a humanized monoclonal antibody that works as an antiangiogenic drug inhibiting vascular endothelial growth factor (VEGF), thereby targeting the high vascularity of glioblastomas (1, 2). Although bevacizumab treatment presents a high radiological response rate of 20–40% (1-3), there are several challenges to its use for the treatment of recurrent glioblastoma, including its short response duration (1-4), limitations in post-treatment tissue confirmation of response, and changes in the behavior of malignant tumors after treatment failure (5, 6). In particular, bevacizumab does not simply reduce angiogenesis but may also trigger treatment failure via several mechanisms, including angiogenesis other than the sprouting pattern of angiogenesis and tumor escape pathways via non-VEGF or VEGF angiogenesis (7-10). This characteristic has become the molecular background for new clinical approaches including combination therapies to overcome the limitations of bevacizumab.

From the radiological aspect, the alteration of

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enhancement or signal intensity patterns on magnetic resonance imaging (MRI) makes it harder to evaluate tumor recurrence after bevacizumab treatment (11-14). Against this background, several studies have tried to classify the radiological recurrence patterns after the failure of bevacizumab treatment for recurrent glioblastoma as these patterns may reflect different biological subgroups requiring specific treatment patterns (4, 11-17). According to these studies, the radiological recurrence patterns after bevacizumab treatment failure differed from those of other conditions in which the treatment did not contain bevacizumab (4, 11-13, 16-28). However, there is no established radiological recurrence pattern to define bevacizumab treatment failure in patients with recurrent glioblastoma; thus, there is no conclusive evidence that the specific patterns of progression after bevacizumab treatment can be associated with patient outcome including survival. Therefore, it is difficult to define a surrogate endpoint in clinical trials. Furthermore, clinical guidelines such as the Response Assessment in Neuro-Oncology, Macdonald, and World Health Organization criteria lack clear descriptions of recurrence patterns. Therefore, categorizing these patterns of progression will allow for more sensitive evaluation of treatment failure and will help to differentiate the findings of progressive disease from other treatment complications.

Therefore, in the present study, a systematic review and meta-analysis of the current literature was performed in an attempt to categorize the radiological patterns of recurrence after bevacizumab treatment and to derive the pooled proportions of patients with recurrent malignant glioma with these different radiological patterns.

MATERIALS AND METHODS

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (29).

Literature Search

A search of the MEDLINE and EMBASE databases was performed to identify original literature reporting radiological recurrence patterns in patients with recurrent malignant glioma after bevacizumab treatment failure. The following search terms were used: ((bevacizumab) OR (avastin) OR (antiangiogenic)) AND ((malignant astrocytoma) OR (high grade glioma) OR (glioblastoma) OR (malignant brain tumor)) AND ((failure) OR (recurrence) OR (resistance) OR (relapse) OR (progression)) AND ((magnetic resonance imaging) OR (MR imaging) OR (MRI) OR (radiology) OR (imaging) OR (image)). A beginning search date was not set and the literature search was updated until April 10, 2019. The search was limited to English-language publications. The bibliographies of relevant articles were also searched to identify additional relevant articles.

Inclusion Criteria

Studies satisfying the following criteria were included: 1) articles using bevacizumab in patients with recurrent malignant glioma; 2) studies classifying radiological recurrence patterns by MRI; 3) availability of sufficient information to calculate the pooled proportions of patients according to radiological recurrence pattern; and 4) original articles.

Exclusion Criteria

Studies or subsets of studies were excluded for any of the following: 1) case reports or case series including fewer than 20 patients; 2) letters, editorials, conference abstracts, systematic reviews or meta-analyses, consensus statements, guidelines, and review articles; 3) articles not focusing on the classification of radiologic recurrence patterns after bevacizumab treatment failure in patients with recurrent high-grade glioma; and 4) articles with, or with suspicion of, overlapping populations.

The literature search and selection were independently performed by two radiologists with 5 and 23 years of experience in brain tumor imaging, respectively.

Data Extraction

The following data were extracted using standardized forms: 1) article characteristics: authors, year of publication, institution, country of origin, duration of patient recruitment, total patient numbers, mean patient age, male-to-female ratio, patient numbers enrolled in the classification of the radiologic pattern of recurrence, and study design; 2) clinical information: analyzed target tumor, criteria for response assessment, history and types of prior treatment before recurrence, combination options with bevacizumab, bevacizumab regimen, and the kinds of chemotherapy agents used with bevacizumab; 3) information about the classification of the radiologic recurrence patterns: MRI sequences used for classification, definitions of the radiologic recurrence patterns, numbers of patients showing each pattern; and 4) progression-

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free survival (PFS) according to the radiologic recurrence pattern.

Quality Assessment

Two reviewers independently performed data extraction and quality assessment using the Risk of Bias for Nonrandomized Studies (RoBANS) tool for nonrandomized controlled trials (30).

Data Synthesis and Analyses

The primary outcome of the current systematic review and meta-analysis was the identification of the pooled proportions according to the radiological recurrence patterns after bevacizumab use. The patterns were categorized as 1) geographically local versus non-local (distant, diffuse, and multifocal according to the classification described by Pope et al. (13)) and 2), for the predominant tumor portion, enhancing tumor versus non-enhancing tumor. In addition, subgroup analysis was performed to evaluate the clinical scenarios of the treatment combination options (bevacizumab treatment only versus bevacizumab combined with cytotoxic chemotherapy) occurring during bevacizumab treatment.

The pooled proportions were calculated using an inverse-variance weighting model (31-33). A random-effects meta-analysis of proportions was used to calculate the overall proportions. Study heterogeneity was evaluated using Higgins inconsistency index (I^2), with substantial heterogeneity indicated by I^2 values above 50% (34). All statistical analyses were conducted by one author (with 1 year of experience in conducting systematic reviews and meta-analyses) using the 'meta' package in R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria)

RESULTS

Literature Search

The article selection process is described in detail in Figure 1. The initial systematic literature search identified 1080 articles. Among these, 582 records were excluded in the MEDLINE and EMBASE database classification systems because they were case reports or case series, letters, editorials, conference abstracts, or review articles. After removing 14 duplicates, screening of the remaining 484 titles and abstracts yielded 30 potentially eligible articles. No additional article was identified in the searches of the bibliographies of these articles. After full-text reviews of the 30 provisionally eligible articles (4, 11-13, 15-28, 35-46), 13 were excluded because they were not in the field of interest (15, 35-41, 43-46) or had populations that were overlapping or had a suspicion of overlapping (42). Finally, the qualitative systematic review and quantitative meta-analysis included 17 studies (4, 11-13, 16-28).

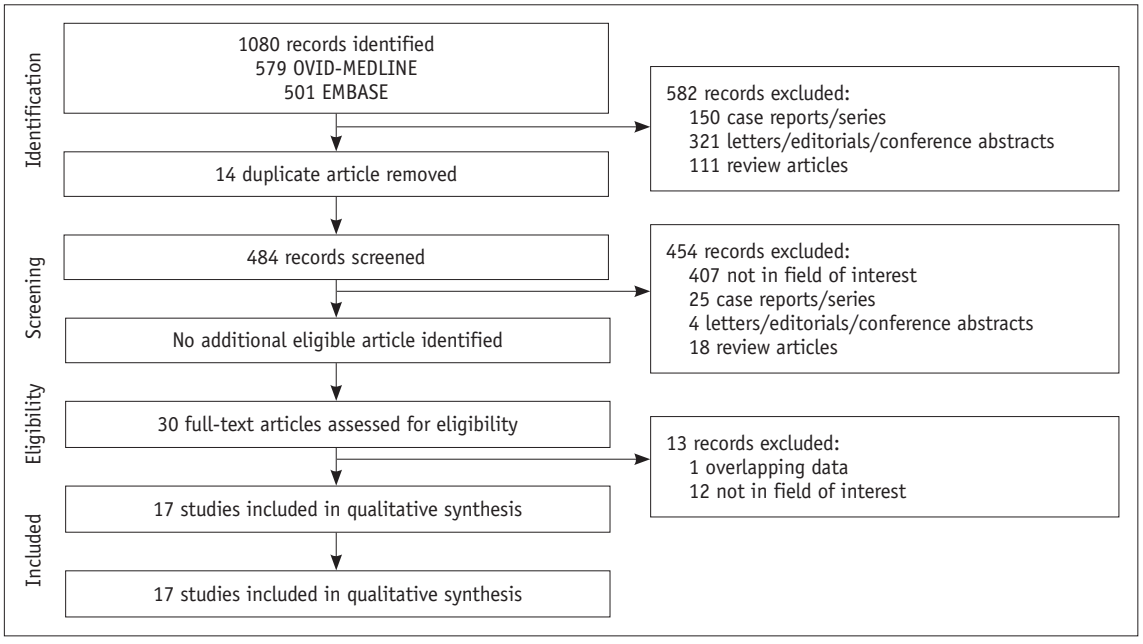

Fig. 1. Flow diagram of study selection process.

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Characteristics of the Included Studies

The detailed characteristics of the included studies are reported in Table 1. The sizes of the original study populations ranged from 24 to 167 patients, with the mean patient ages ranging from 47–58 years, and the sizes of the populations included in the pooled analysis of the radiological patterns of recurrence ranging from 14 to 124 patients. Only one article reported a prospective study (24); the other studies were retrospective (4, 11-13, 16-23, 25-28). Seven studies included recurrent high-grade glioma (4, 16, 18, 23, 25, 26, 28) while the other 10 studies specifically included recurrent glioblastoma (11-13, 17, 19-22, 24, 27). The tumor response assessment criteria used after treatment varied according to the center from which the studies originated, as described in Table 1. The treatment strategies were also heterogeneous (Table 2). In terms of prior treatment history before bevacizumab, eight studies included patients having undergone surgery, chemotherapy, and radiation therapy (4, 11, 13, 18-21, 23, 24, 28); four studies included chemotherapy and radiation therapy (17, 22, 26, 27); two studies included chemotherapy (12, 16); and one study included radiation therapy (25). Four studies also included patients with a prior treatment history with an antiangiogenic agent (16, 21, 26, 28). Regarding combination options during bevacizumab treatment, eight studies included both patients treated with bevacizumab only and with bevacizumab in combination with chemotherapy (4, 11, 13, 18, 19, 26-28); four studies included only patients treated with bevacizumab in combination with chemotherapy (16, 21, 22, 24); two studies included only patients treated with bevacizumab only (12, 20); and one study included patients treated with bevacizumab only, with bevacizumab in combination with radiation therapy, and bevacizumab in combination with chemotherapy (17). One study did not provide detailed information on the treatment combination (23). The studies commonly tried to classify the radiological recurrence patterns after bevacizumab treatment failure according to its geographical distribution. Some studies also tried to categorize the predominant tumor portion as non-enhancing or enhancing (4, 11, 12, 16, 17, 21-23, 26-28).

Proportions according to the Radiologic Recurrence Pattern

The pooled proportion of a geographical radiological pattern of non-local recurrence was 38.3% (95% confidence interval [CI], 30.6–46.1%; the rates of distant, diffuse, and multifocal patterns were 6.7%, 29.2%, and 4.1%, respectively) (Table 3, Fig. 2). Study heterogeneity was substantial in the analysis (I^2 = 77.7%) The pooled proportion of non-enhancing tumors with a predominant radiologic recurrence pattern was 34.2% (95% CI, 27.3–41.5%). The study heterogeneity was borderline in this analysis (I^2 = 50.1%)

Subgroup Analysis

The pooled proportions of a geographical radiological pattern of non-local recurrence was 34.9% (95% CI, 22.8–49.4%) among the 222 patients treated with bevacizumab only (four studies) and 22.5% (95% CI, 9.5–44.6%) in the 264 patients treated with the combination with cytotoxic chemotherapy (seven studies).

PFS according to Radiologic Recurrence Pattern

We extracted PFS according to the radiologic recurrence patterns from the three enrolled studies for which this information was available (11, 19, 23). The PFS of local recurrence tended to be shorter than that for non-local recurrence according to the radiological recurrence pattern in the two studies, with unknown significance (local vs. non-local recurrence; 4.9 vs. 6.3 months and 3.9 vs. 4.2 months for the two studies). One study reported discordant data (local vs. non-local recurrence; 3.7 vs. 4.2 months) (23).

Quality Assessment of the Studies

The quality of the included studies was assessed according to the RoBANS criteria, the results of which are presented in Figure 3. All studies showed a low risk of bias in participant comparability, incomplete outcome data, outcome evaluation, confounding variables, and participant comparability. However, 12 of the 17 studies showed an unclear risk of bias in the blinding of participants and personnel domain, as they did not make clear statements in this regard (4, 16-20, 22-25, 27, 28). In the measurement of exposure domain, five studies showed a low risk of bias as multiple readers performed the radiologic assessment (11, 12, 17, 21, 26), five of 17 studies showed a high risk of bias because only a single reader assessed the radiologic response (13, 16, 20, 22, 24), and the other seven studies showed an unclear risk of bias (4, 18, 19, 23, 25, 27, 28). Finally, in the selection of patients domain, only one study showed a low risk of bias because of its prospective design (24) while the others showed high risks of bias due to their retrospective designs (4, 11-13, 16-23, 25-28).

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Table 1. Characteristics of Included Studies

Source	Affiliation	Duration of Patient Recruitment	Patient No. Total	Mean Age (Years)	Male: Female	Patient No. Radiological Recurrence Patterns	Study Design	Target Tumors Analyzed	Response Assessment
Barajas et al., 2016 (18)	Oregon Health & Science University, USA	Unclear	26	52.6	13:13	26	Retrospective	Recurrent HGG	T2 FLAIR and contrast enhancement volume and/or worsening neurologic status
Bloch et al., 2013 (19)	University of California, USA	2005–2009	81	53.8	44:27	71	Retrospective	Recurrent glioblastoma	RANO criteria + multi-disciplinary clinical assessment
Cachia et al., 2017 (11)	Medical University of South Carolina, USA	January 2010–July 2014	64	51.5	38:26	64	Retrospective	Recurrent glioblastoma	RANO criteria
Chamberlain, 2011 (20)	University of Washington, USA	Unclear	80	57.2	50:30	80	Retrospective	Recurrent glioblastoma	NA
Desjardins et al., 2012 (21)	Duke University Medical Center, USA	July 2007–October 2007	32	56.4	19:13	21	Retrospective	Recurrent glioblastoma	Modified Macdonald criteria
Gállego Pérez-Larraya et al., 2012 (22)	Boulevard de l'Hôpital, France	May 2007–January 2010	78	58.3	48:30	58	Retrospective	Recurrent glioblastoma	RECIST + FLAIR + RANO criteria
Iwamoto et al., 2009 (17)	Memorial Sloan-Kettering Cancer Center, USA	October 2006–January 2009	37	54.3	26:11	36	Retrospective	Recurrent glioblastoma	Macdonald criteria + FLAIR
Kim et al., 2015 (23)	Samsung Medical Center, Seoul National University, Korea	September 2008–September 2014	71	47.3	36:28 (for 64)	64	Retrospective	Recurrent HGG	RANO criteria
Kim et al., 2017 (4)	Chonnam National University, Korea	August 2011–November 2015	24	47.5	10:14	20	Retrospective	Recurrent HGG	RANO criteria
Narayana et al., 2009 (24)	New York University Medical Center, USA	January 2005–June 2007	61	56.1	39:22	50	Prospective	Recurrent glioblastoma	Macdonald criteria
Niyazi et al., 2014 (25)	University Hospital of Munich, Germany	August 2008–July 2012	31	51.3	21:10	31	Retrospective	Recurrent HGG	RANO criteria
Norden et al., 2008 (26)	Dana-Farber/Brigham and Women's Cancer Center and Harvard Medical School, USA	June 2005–March 2007	55	50.2	32:23	26	Retrospective	Recurrent HGG	Macdonald criteria
Nowosielski et al., 2014 (12)	Innsbruck Medical University, Austria; Heidelberg University, Germany	August 2007–January 2013	83	53.1	24:59	83	Retrospective	Recurrent glioblastoma	RANO criteria
Pope et al., 2011 (13)	University of California Los Angeles, USA	July 2006–September 2007	167	55.2	69:31	124	Retrospective	Recurrent glioblastoma	WHO response evaluation criteria
Schaub et al., 2013 (27)	University of Bonn Medical Center, Germany	January 2008–December 2009	26	NA	20:6	26	Retrospective	Recurrent glioblastoma	RANO criteria
Thomas et al., 2018 (28)	Memorial Sloan-Kettering Cancer Center, USA	Unclear	32	56.4	25:7	32	Retrospective	Recurrent HGG	NA
Zuniga et al., 2009 (16)	Henry Ford Health System, USA	November 2005–April 2008	51	51.1–53.2	33:18	38	Retrospective	Recurrent HGG	Macdonald criteria

FLAIR = fluid-attenuated inversion recovery, HGG = high grade glioma, NA = not available, RANO = Response Assessment in Neuro-Oncology, RECIST = response evaluation criteria in solid tumors, WHO = World Health Organization

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Table 2. Details of Clinical and Radiologic Examinations of Included Studies

Source	Treatment History Prior to Bevacizumab				Combination Options with Bevacizumab			Regimen of Bevacizumab	Chemo-Agents with Bevacizumab	Sequences Used in Classification of Radiologic Recurrence Pattern			Classification of Radiologic Recurrence Pattern
	Op.	RTx.	CTx.	Anti-Angio	Only	With RTx.	With CTx.			CE-T1WI	T2/FLAIR	DWI	
Barajas et al., 2016 (18)	Y	Y	Y	NA	Y	N	Y	10 mg/kg, every 2 weeks	CPT, TMZ	Y	Y	Y	'Edematous,' 'Infiltrative' 'Salt and pepper,' and 'Block' on DWI
Bloch et al., 2013 (19)	Y	Y	Y	NA	Y	N	Y	10 mg/kg, every 2 weeks	CPT, erlotinib, irinotecan, lomustine, TMZ	Y	Y	N	'Focal' (< 2 cm from original tumor) 'Disseminated' (> 2 cm from original tumor, contralateral, multifocal) 'Nodular,' 'Diffuse patchy,' and 'Non-enhancing' for 'Disseminated'
Cachia et al., 2017 (11)	Y	Y	Y	N	Y	N	Y	NA	Irinotecan, lomustine, SPT, TPI-287, TMZ, vorinostat	Y	Y	N	Two classification schemes: 1. by Nowosielski et al. (12): 'T2-diffuse,' 'Contrast T1 flare-up,' 'Non-responder,' and 'T2-circumscribed' 2. by modified Pope et al. (13): classification: 'Local,' 'Diffuse,' and 'Distant'
Chamberlain, 2011 (20)	Y	Y	Y	NA	Y	N	N	NA	NA	Y	Y	N	By Pope et al. (13): 'Local,' 'Distant,' 'Multifocal,' and 'Diffuse'
Desjardins et al., 2012 (21)	Y	Y	Y	Partial	N	N	Y	NA	TMZ	Y	Y	N	By Pope et al. (13): 'Local,' 'Distant,' 'Multifocal,' and 'Diffuse'
Gállego Pérez-Larraya et al., 2012 (22)	NA	Y	Y	NA	N	N	Y	NA	Irinotecan	Y	Y	N	By Norden et al. (26) and Zuniga et al. (16): 'Local contrast-enhanced recurrence,' 'New distant foci of enhancement,' and 'Diffuse'
Iwamoto et al., 2009 (17)	NA	Y	Y	NA	Y	Y	Y	NA	Irinotecan, TMZ	Y	Y	N	'Local,' 'Predominantly non-enhancing,' and 'New multifocal enhancement'
Kim et al., 2015 (23)	Y	Y	Y	NA	NA	NA	NA	NA	NA	Y	Y	N	By Nowosielski et al. (12): 'T2-diffuse,' 'Contrast T1 flare-up,' and 'Non-responder'
Kim et al., 2017 (4)	Y	Y	Y	NA	Y	N	Y	10 mg/kg, every 2 weeks	Irinotecan	Y	Y	N	'Focal' and 'Diffuse'
Narayana et al., 2009 (24)	Y	Y	Y	NA	N	N	Y	NA	CPT, irinotecan	Y	Y	N	'Local,' 'Extensive gliomatosis,' and 'Diffuse without original lesion site'
Niyazi et al., 2014 (25)	NA	Y	NA	NA	N	Y	N	NA	NA	Y	Y	N	'In-field' and 'Ex-field'
Norden et al., 2008 (26)	NA	Y	Y	Partial	Y	N	Y	10 mg/kg, every 2 weeks	CPT, carmustine, ironotecan, TMZ	Y	Y	N	'Local (enhancement developed in contiguity with original tumor),' 'Distant (new foci of enhancement distant from original tumor),' and 'Diffuse (25% increase on FLAIR)'
Nowosielski et al., 2014 (12)	N	N	Y	NA	Y	N	N	10 mg/kg, every 2 weeks	NA	Y	Y	N	'T2-diffuse (mainly T2 ill-defined diffuse infiltration),' 'Contrast T1 flare-up (increased enhancement again),' 'Non-responder,' and 'T2-circumscribed (mainly local non-enhancing tumor)'

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DISCUSSION

The current systematic review and meta-analysis showed pooled proportions of 38.3% (95% CI, 30.6–46.1%) and 34.2% (95% CI, 27.3–41.5%) for a geographical radiologic pattern of non-local recurrence and a non-enhancing tumor-

Table 2. Details of Clinical and Radiologic Examinations of Included Studies (Continued)

Source	Treatment History Prior to Bevacizumab				Combination Options with Bevacizumab			Regimen of Bevacizumab	Chemo-Agents with Bevacizumab	Sequences Used in Classification of Radiologic Recurrence Pattern			Classification of Radiologic Recurrence Pattern
	Op.	RTx.	CTx.	Anti-Angio	Only	With RTx.	With CTx.			CE-T1WI	T2/FLAIR	DWI	
Pope et al., 2011 (13)	Y	Y	Y	N	Y	N	Y	10 mg/kg, every 2 weeks	CPT	Y	Y	N	'Local (< 3 cm from tumor),' 'Distant (> 3 cm separate from tumor, single),' 'Multifocal (more than one enhancement foci),' and 'Diffuse (> 3 cm extending from tumor, single)'
Schaub et al., 2013 (27)	NA	Y	Y	N	Y	N	Y	10 mg/kg, every 2 weeks	Irinotecan	Y	Y	N	'Primary progressive,' 'FLAIR-only progression (mainly on T2/FLAIR)'
Thomas et al., 2018 (28)	Y	Y	Y	Partial	Y	N	Y	10 mg/kg, every 2 weeks	Ironotecan, lomustine, TMZ	Y	Y	N	'Local enhancement,' Distant enhancement,' 'Diffuse non-enhancing,' and 'Diffuse leptomeningeal'
Zuniga et al., 2009 (16)	NA	NA	Y	Partial	N	N	Y	NA	Irinotecan	Y	Y	N	'Local (< 2 cm from tumor),' 'Distant (at least one new foci of enhancement, > 2 cm from tumor),' and 'Diffuse (mainly on FLAIR)'

CE-T1WI = contrast-enhanced T1 weighted image, CPT = cisplantin, CTx. = chemotherapy, DWI = diffusion weighted image, N = not used, Op. = operation, RTx. = radiation therapy, TMZ = temozolomide, T2/FLAIR: T2 weighted image/fluid attenuated inversion recovery, Y = used

Table 3. Meta-Analytic Proportions of Radiologic Recurrence Patterns after Failure of Bevacizumab Treatment

Source	Local	Non-Local			Total	Predominant Enhancing	Predominant Non-Enhancing	Total
		Distant	Diffuse	Multifocal				
Barajas et al., 2016 (18)	10	0	16	0	26	NA	NA	NA
Bloch et al., 2013 (19)	59	0	8	4	71	NA	NA	NA
Cachia et al., 2017 (11)	35	15	14	0	64	21	14	35
Chamberlain, 2011 (20)	57	7	9	7	80	NA	NA	NA
Desjardins et al., 2012 (21)	11	2	8	0	21	16	5	21
Gállego Pérez-Larraya et al., 2012 (22)	28	11	17	0	56	28	17	45
Iwamoto et al., 2009 (17)	17	0	13	6	36	23	13	36
Kim et al., 2015 (23)	25	0	18	0	43	25	18	43
Kim et al., 2017 (4)	11	0	3	0	14	8	6	14
Narayana et al., 2009 (24)	35	1	14	0	50	NA	NA	NA
Niyazi et al., 2014 (25)	26	5	0	0	31	NA	NA	NA
Norden et al., 2008 (26)	16	4	4	0	24	20	4	24
Nowosielski et al., 2014 (12)	52	0	15	0	67	51	15	67
Pope et al., 2011 (13)	55	2	62	5	124	NA	NA	NA
Schaub et al., 2013 (27)	11	0	6	0	17	11	6	17
Thomas et al., 2018 (28)	23	1	8	0	32	25	7	32
Zuniga et al., 2009 (16)	13	4	21	0	38	17	21	38
Pooled proportions (%)	61.7	6.7	29.2	4.1	100	65.5	34.2	100
	61.7		38.3		100			100
95% CI	53.9–69.5		30.6–46.1			58.1–72.1	27.3–41.5	

CI = confidence interval

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predominant recurrence pattern, respectively. These findings of the existence and proportions of different types of recurrence provide comprehensive information on patients with recurrent high-grade glioma after bevacizumab treatment and could provide insights into surrogate endpoints for treatment failure in clinical trials of recurrent high-grade glioma.

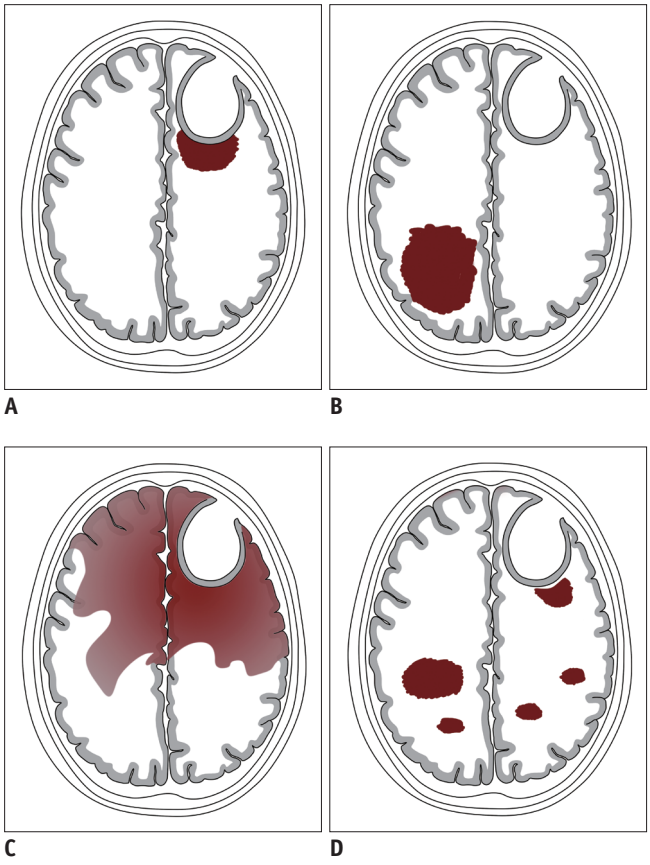

Fig. 2. Illustration of geographic radiological patterns of recurrence.
A. Local. **B.** Distant. **C.** Diffuse. **D.** Multifocal (**B-D**: non-local).

The clinical and radiological challenges in the use of bevacizumab for the treatment of recurrent glioblastoma include the short response duration (less than 20 weeks), the short median overall survival (ranging from 31 to 74 weeks), and the difficulty in tissue confirmation for both patients and clinicians (1-4). Potential changes in enhancement or signal intensity patterns on MRI make it difficult to evaluate radiological recurrence (11-14). Several studies included in this systematic review and meta-analysis tried to classify the radiologic recurrence patterns after bevacizumab treatment failure in recurrent glioblastoma (4, 11-13, 16-28). Although these categorization methods mostly focused on the location and enhancement of recurrent disease, the categorization systems differed. Therefore, we need to organize the recurrence patterns systematically. In this systematic review and meta-analysis, the proportions of non-local tumor recurrence and non-enhancing tumor recurrence were substantial, at 38.3% and 34.2%, respectively.

Bevacizumab may alter tumor behavior due to its mechanism of action, which makes it harder to assess tumor response and detect treatment failure (5, 6). Regarding assessment of tumor response, several recent studies have shown that bevacizumab did not simply reduce tumor vascularity but rather normalized the microvascular environment and improved the distribution of the blood supply while also reducing tumor-associated edema or local inhomogeneity, reducing tissue hypoxia, and sensitizing the tumor to other treatments including radiation therapy, chemotherapy, and immunotherapy (47-49). Second, owing to its mechanism of action, recurrence on bevacizumab

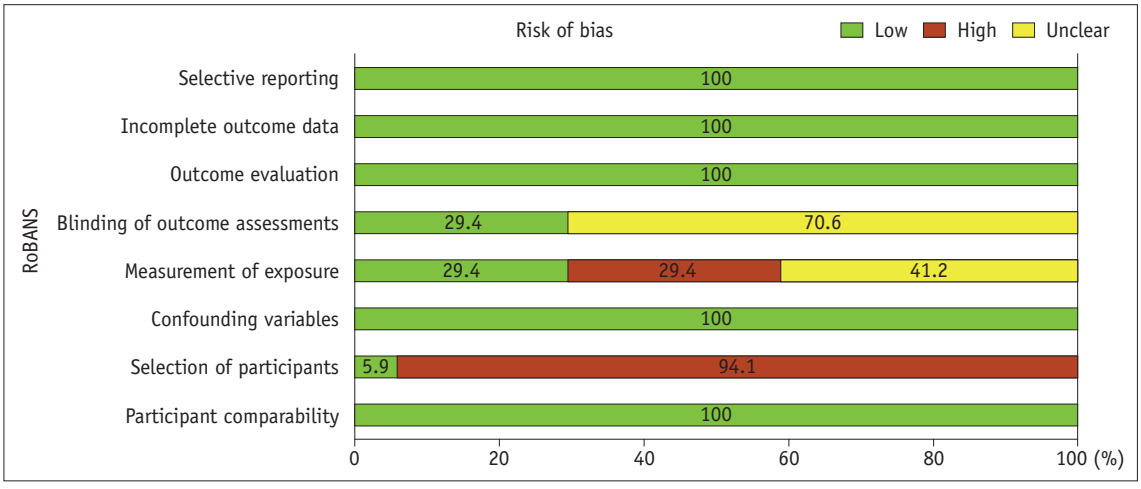

Fig. 3. Quality assessment of included studies according to RoBANS tool. RoBANS = Risk of Bias for Nonrandomized Studies

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is often non-enhancing, distant, or diffuse disease. A non-enhancing, distant recurrence may be suggestive of a transition to a more aggressive phenotype (26, 50), although this suggestion remains controversial. Additionally, resistance to bevacizumab may occur, resulting in treatment failure. The reason for this resistance is unclear but may be mainly due to the complexity of the mechanism and the multiple bypass pathways at the molecular and angiogenesis level after bevacizumab use (7-10). Although no conclusive evidence supports that specific patterns of progression after bevacizumab treatment are associated with patient outcomes including survival, recognizing these patterns of progression will allow a more sensitive evaluation of treatment failure and will help to differentiate findings of progressive disease from other treatment complications.

Accurate assessment of treatment response is important because several studies have shown radiographic response to bevacizumab is correlated to PFS or overall survival (42, 51). However, the data are insufficient to determine changes in PFS according to the recurrence pattern. Several studies reported a relatively longer PFS for non-local recurrence than that for local tumor recurrence, while one study reported a discordant tendency (11, 19, 23). According to Nowosielski et al. (12), overall survival may be reflected by the recurrence patterns at the time recurrence diagnosis. Recently, non-local or non-enhancing tumor recurrence was suggested to be correlated with angiogenesis types such as 'vessel co-option' and 'glioma stem-like cells,' rather than with the 'sprouting' pattern of angiogenesis that is the target of bevacizumab (8). These results indicate that the patterns reflect different biological subgroups that should be addressed appropriately, according to their specific patterns. However, there were limitations in obtaining sufficient meta-analytic evidence regarding etiology due to the heterogeneity among the enrolled studies including response assessment criteria, treatment history prior to bevacizumab, various combination regimens of chemotherapy, etc. Further clarification with survival data analysis according to the radiologic patterns of recurrence and demonstration of the etiologies for the heterogeneity are needed.

This study has several limitations. First, the definitions of the classifications of radiologic patterns of recurrence after bevacizumab were not the same across studies. However, we tried to categorize them in our definitions of geographical and predominant tumor portion patterns. Second, each of the studies included a limited number of patients due to the scarcity of recurrent malignant glioma, which caused a reduction in the variety of endpoints assessed in this meta-analysis and which could be an important issue in the assessment of recurrence after bevacizumab in patients with recurrent high-grade glioma. Further investigation is needed. In addition, most studies were retrospective, resulting in a risk of bias in patient selection.

In conclusion, a substantial proportion of high-grade glioma patients showed non-local or non-enhancing radiologic patterns of recurrence after bevacizumab treatment. The identification of the radiologic pattern of recurrence could provide insight into surrogate endpoints of treatment failure in clinical trials of recurrent high-grade glioma.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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