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Bevacizumab Alone Versus Bevacizumab Plus Irinotecan in Patients With Recurrent Glioblastoma: A Nationwide Population-Based Study

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ABSTRACT

Background: For treating recurrent glioblastoma, for which there is no established treatment, the antiangiogenic antibody, bevacizumab, is used alone or with irinotecan. This study was aimed at comparing the survival of patients with recurrent glioblastoma receiving bevacizumab monotherapy and those receiving bevacizumab plus irinotecan combination therapy (B+I) by using a nationwide population-based dataset.
Methods: Patients matching the International Classification of Diseases code C71.x were screened from the Health Insurance Review and Assessment Service database. From January 2008 to November 2021, patients who underwent surgery or biopsy and subsequent standard concurrent chemoradiation with temozolomide were included. Among them, those who received bevacizumab monotherapy or B+I were selected. Demographic characteristics, inpatient stay, prescription frequency, survival outcomes, and steroid prescription duration were compared between these two groups.
Results: Eight hundred and forty-six patients who underwent surgery or biopsy and received concurrent chemoradiotherapy with temozolomide were included. Of these, 450 and 396 received bevacizumab monotherapy and B+I, respectively. The corresponding median overall survival from the initial surgery was 22.60 months (95% confidence interval [CI], 20.50–24.21) and 20.44 months (95% CI, 18.55–22.60; $P = 0.508$, log-rank test). The B+I group had significantly more bevacizumab prescriptions (median 5 times; BEV group: median 3 times). Cox analysis, based on the postsurgery period, revealed that male sex (hazard ratio [HR], 1.28; $P = 0.002$), older age (HR, 1.01; $P = 0.042$), and undergoing biopsy instead of surgery (HR, 1.79; $P < 0.0001$) were significantly associated with decreased survival. Fewer radiotherapy cycles correlated with improved survival outcomes (HR, 0.63; $P = 0.001$). Cox analysis, conducted from the start of chemotherapy including bevacizumab, showed that male sex was the only variable significantly associated with decreased survival (HR, 1.18; $P = 0.044$).
Conclusion: We found no significant difference in overall survival between the bevacizumab monotherapy and B+I groups. Considering the additional potential toxicity associated with irinotecan, bevacizumab monotherapy could be a suitable treatment option for treating recurrent glioblastoma.

Keywords: Bevacizumab; Glioblastoma; Irinotecan; Survival Analysis; Chemoradiotherapy

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Roh TH. Data curation: Lee E. Formal analysis: Lee E. Funding acquisition: Kim SH, Roh TH. Investigation: Roh TH. Methodology: Lee E, Roh TH. Project administration: Roh TH. Resources: Roh TH. Supervision: Roh TH. Validation: Kim SH. Visualization: Lee E. Writing - original draft: Lee Y. Writing - review & editing: Roh TH.

INTRODUCTION

Glioblastoma is the most aggressive and common primary brain tumor in adults, with a median survival time of 12–15 months despite standard treatment. The current standard of care for newly diagnosed glioblastoma includes maximal safe surgical resection followed by concurrent chemoradiotherapy with temozolomide and adjuvant temozolomide.[1-3] However, most patients experience tumor recurrence and the prognosis remains poor. Various therapeutic strategies have been explored for recurrent glioblastoma, including re-resection, re-irradiation, and systemic treatments with targeted agents or chemotherapy.[4-6]

Bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor, has demonstrated benefits in patients with recurrent glioblastoma, in terms of progression-free survival and quality of life. Vascular endothelial growth factor plays a crucial role in tumor angiogenesis and vascular permeability, contributing to tumor growth and progression. By inhibiting vascular endothelial growth factor, bevacizumab reduces tumor vascularization, normalizes the tumor vasculature, and potentially enhances the delivery of chemotherapy to the tumor.[7-9]

Irinotecan, a topoisomerase I inhibitor, is a chemotherapeutic agent that has demonstrated activity in various solid tumors, including glioblastoma. Studies have been conducted to test the effect of administering irinotecan to patients with recurrent glioblastoma, despite standard treatments including temozolomide administration, because irinotecan has a different mechanism of action from that of alkylating agents such as temozolomide.[10,11] Synergistic effects were found when bevacizumab was administered in combination with other anticancer drugs, particularly irinotecan, in patients with colorectal, lung, and breast cancers.[12-14] This combined treatment approach has also been attempted in patients with recurrent glioblastoma.[15-25] However, it has not yet been proven that there is a difference in overall survival between monotherapy with bevacizumab and the combination therapy with bevacizumab and irinotecan.[26-29]

Owing to the lack of large-scale, multi-institutional, prospective studies, most patients with recurrent glioblastoma receive bevacizumab monotherapy or combination therapy with bevacizumab and irinotecan without a standardized guideline, largely driven by clinician preferences and beliefs about treatment efficacy. In this study, we aimed to address these limitations by conducting a large-scale retrospective analysis using data from the Health Insurance Review and Assessment Service (HIRA) database to compare the outcomes of bevacizumab monotherapy and bevacizumab plus irinotecan combination therapy for recurrent glioblastoma.

METHODS

Data from the Korean HIRA database were used to evaluate and compare the treatment effects of bevacizumab monotherapy and bevacizumab plus irinotecan combination therapy for patients with recurrent glioblastoma.

Data collection

Data on patients diagnosed with the International Classification of Diseases-10 (ICD-10) code C71.x were collected from January 2007 to November 2021. Those who underwent

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craniotomy and tumor removal (codes: S4634, S4635, S4636, S4637) or biopsy (code: S4756) and received concurrent temozolomide chemotherapy (ingredient code: 358202ACH, 358203ACH, 358204ACH) and radiation therapy within 6 weeks after surgery were included. To ensure the accuracy of the study cohort, patients diagnosed after January 2008 and who did not have any surgical codes recorded between 2007 and 2008 were specifically selected, further refining the study population to those whose surgical interventions were fully captured within the study period. Patients were excluded if they were under 18 years of age at the time of the initial diagnosis, if the time difference between the initial diagnosis and the start of radiation and chemotherapy treatment was more than 6 weeks, if the time difference between the initial diagnosis and surgery was more than 90 days, if they did not complete at least 30 days of chemotherapy and radiation treatment, if they died within 90 days after surgery, or if they developed another malignancy.

Patients were further categorized into two groups based on their treatment at the time of recurrence: bevacizumab monotherapy and bevacizumab plus irinotecan combination therapy groups. The bevacizumab monotherapy group included patients who started bevacizumab treatment at the time of recurrence with an aseptic preparation of injectable antineoplastic agents (EDI code: J0041) or manual puncture injection of intravenous antineoplastic agents (EDI code: KK153) and no other antineoplastic agents or only bevacizumab (ingredient codes: 554330BIJ, 554331BIJ). The bevacizumab plus irinotecan combination therapy group included patients who started bevacizumab plus irinotecan treatment at the time of recurrence, with an aseptic preparation of injectable antineoplastic agents (EDI code: J0041) or manual puncture injection of intravenous antineoplastic agents (EDI code: KK153) and with only irinotecan (ingredient codes: 177430BIJ, 177431BIJ, 177433BIJ, 177435BIJ, 666002BIJ) or both irinotecan and bevacizumab.

In South Korea, the use of anticancer drugs for specific diseases is strictly regulated. bevacizumab is the only approved intravenous anticancer drug for glioblastoma, and its use is limited to either monotherapy or combination therapy with irinotecan. The drug is currently approved for use in cases of recurrence after standard therapy or for radiation necrosis refractory to conservative treatment. Therefore, to identify patients with recurrent glioblastoma treated with bevacizumab, patients with the J0041 and KK153 codes were identified. Those who also received irinotecan were identified through the ingredient code for irinotecan. The codes used are detailed in **Supplementary Table 1**. Cases considered as instances of regimen switching, such as those where irinotecan was added during the administration of bevacizumab, or cases where irinotecan was discontinued while administering bevacizumab plus irinotecan were excluded.

Variables assessed

A range of variables were assessed, including follow-up time; sex; age; time from diagnosis to surgery; time from surgery to chemotherapy (bevacizumab or bevacizumab plus irinotecan); number of radiation therapy cycles; number of adjuvant temozolomide therapy cycles; duration of steroid prescription; inpatient days since surgery at tertiary, general, or nursing hospitals; number of bevacizumab administration cycles; seizure history before surgery; hypertension status; and diabetes mellitus status. Radiation therapy was considered as one course if code HD061 or HZ271 was present at least 10 times within 30 consecutive days, and a gap of 60 days or more between the HD061 and HZ271 codes was required for the therapy to be considered as two or more courses. An adjuvant temozolomide cycle was defined as a 28-day rest period after concurrent chemoradiation, followed by a 5-day temozolomide

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administration cycle. Steroid prescription duration was calculated using dexamethasone and prednisolone ingredient codes for both oral and injectable forms.

Endpoints

The primary endpoint of the study was to determine if there was a difference in overall survival between the bevacizumab and bevacizumab plus irinotecan groups. Overall survival from the time of surgery as well as from the initiation of chemotherapy including bevacizumab were compared. The secondary endpoints included comparisons between the two groups in terms of the following aspects: differences in the number of inpatient days and differences in the duration of steroid use.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and treatment modalities. Continuous variables are presented as means and standard deviations, while categorical variables are presented as frequencies and percentages. Differences between the two groups were analyzed using the independent *t*-test or the Mann-Whitney *U* test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, depending on data distribution. To compare overall survival between the two groups, Kaplan-Meier survival curves were generated, and the log-rank test was applied to assess the statistical significance of any observed differences. Univariate and multivariate Cox proportional hazard regression models were used to estimate hazard ratios and 95% confidence intervals (CIs), adjusting for potential confounding factors. All statistical tests were two-sided; a *P* value of less than 0.05 was considered statistically significant.

Ethics statement

This study was conducted in accordance with the ethical guidelines for human subject research and approved by the Institutional Review Board of the Ajou University Hospital (IRB code: AJOUIRB-EX-2022-314). Informed consent was waived because of the retrospective nature of the study. The study protocol, data collection, and analysis procedures were reviewed and approved to ensure the protection of the rights and welfare of the study participants.

RESULTS

Population characteristics and demographics

We conducted a retrospective study using data from the HIRA database on patients diagnosed with glioblastoma (C71.x) between January 2008 and November 2021. It is estimated that 8,738 patients were diagnosed with glioblastoma during this period. Of the 8,738 selected patients, 5,098 had undergone surgical removal or biopsy and received radiation therapy within 6 weeks, indicating that they received standard treatment. After excluding patients who met the exclusion criteria from among those selected, 1,046 patients were found to have been administered bevacizumab. We further excluded 200 patients for whom regimens had been switched. Of these patients, for 180 (90%) patients, treatment was switched from bevacizumab plus irinotecan to bevacizumab, while for 20 patients (10%), the opposite was true. Our final study population comprised 846 patients. Among the patients included, 450 (53%) and 396 (47%) were in the bevacizumab and bevacizumab plus irinotecan groups, respectively (**Fig. 1**).

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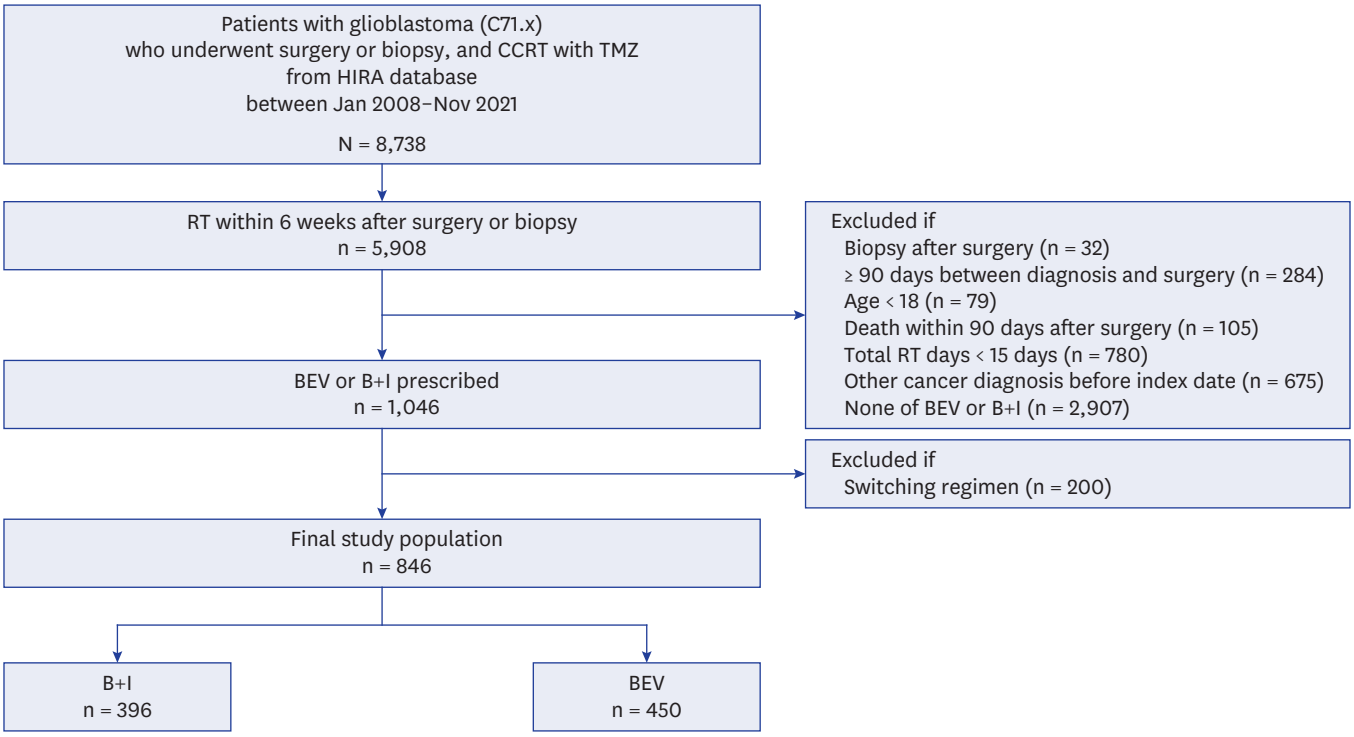

Fig. 1. Flow chart of patient selection.
CCRT = concurrent chemoradiation therapy, TMZ = temozolomide, HIRA = Health Insurance Review and Assessment Service, RT = radiation therapy, BEV = bevacizumab monotherapy, B+I = bevacizumab plus irinotecan combination therapy.

There was no significant difference in the median follow-up time (18.53 months) between the two groups ($P = 0.462$). However, there were significant intergroup differences in terms of sex and age. The bevacizumab group had a higher percentage of women (50.22%) than in the bevacizumab plus irinotecan group (42.68%). The mean age of the bevacizumab group (54.50 years) was higher than that of the bevacizumab plus irinotecan group (51.98 years). The median time from diagnosis to surgery and from surgery to chemotherapy was similar across both groups. Surgical removal was the primary intervention in 92.67% of the cases, while biopsy accounted for 7.33%. There were no significant intergroup differences in the numbers of radiation and adjuvant temozolomide therapy cycles (**Table 1**).

The duration of steroid prescriptions was similar between the groups. The bevacizumab plus irinotecan group had significantly shorter overall inpatient stays than the BEV group (112 vs. 152 days, $P < 0.0001$), particularly in a general hospital setting (27 vs. 52.5 days, $P < 0.0001$). Bevacizumab prescription frequency was significantly higher in the bevacizumab plus irinotecan group than in the bevacizumab group (5 vs. 3 times, $P < 0.001$). There were no significant intergroup differences in the history of seizures, hypertension, and diabetes mellitus (**Table 1**).

Survival analysis

The results of the survival analysis indicated that the 50% survival estimates were 22.60 months (95% CI, 20.50–24.21) and 20.44 months (95% CI, 18.55–22.60) in the bevacizumab and bevacizumab plus irinotecan groups, respectively. The log-rank test was performed to compare the survival times between the groups from the time of surgery and initiation of chemotherapy including bevacizumab; however, intergroup differences were not significant.

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Table 1. Baseline characteristics and demographics

Characteristics	All (N = 846)	B+I (n = 396)	BEV (n = 450)	*P* value
Follow-up time, mon	18.53 [12.88–31.01]	18.05 [13.04–31.21]	19.24 [12.81–30.78]	0.462
Sex				**0.028**
Male	451 (53.31)	227 (57.32)	224 (49.78)	
Female	395 (46.69)	169 (42.68)	226 (50.22)	
Age, yr	53.32 ± 12.39	51.98 ± 12.15	54.50 ± 12.49	**0.003**
Time to surgery from diagnosis, days	3 [0–9]	3 [0–8]	3 [0–10]	0.062
Time to bevacizumab included chemotherapy from surgery, mon	11.2 [7.36–19.29]	11.07 [7.36–19.01]	11.29 [7.46–19.29]	0.981
Type of surgery				0.287
Resection	784 (92.67)	371 (93.69)	413 (91.78)	
Biopsy	62 (7.33)	25 (6.31)	37 (8.22)	
No of RT cycle	1.12 (0.33)	1.12 (0.33)	1.13 (0.33)	0.811
No of adjuvant TMZ cycles (n = 762)				
Mean ±	4.64 ± 1.75	4.71 ± 1.76	4.58 ± 1.74	0.309
< 3	126 (16.54)	58 (16.16)	68 (16.87)	0.790
≥ 3	636 (83.46)	301 (83.84)	335 (83.13)	
Days of steroid prescription				
Dexamethasone (n = 781)	53 [23–105]	53 [23–110]	52.5 [24–100]	0.692
Prednisolone (n = 692)	55 [11–180]	60.5 [12–195]	53 [10–163]	0.324
Inpatient days since surgery				
Tertiary hospital (n = 754)	49 [23–102]	46.5 [24–94.5]	50.5 [23–120]	0.380
General hospital (n = 520)	42 [12–96.5]	27 [8.5–64.5]	52.5 [18–113.5]	**< 0.0001**
Nursing hospital (n = 361)	47 [18–116]	40.5 [18–98.5]	52 [18–135]	0.098
All hospital	136 [68–229]	112 [60–203.5]	152.5 [76–273]	**< 0.0001**
Bevacizumab	4 [2–8]	5 [2–8]	3 [1–7]	**< 0.0001**
Seizure before surgery	264 (31.21)	130 (32.83)	134 (29.78)	0.339
Hypertension	252 (29.79)	108 (27.27)	144 (32.00)	0.134
DM	104 (12.29)	43 (10.86)	61 (13.56)	0.233

Values are presented as median [interquartile range] or number (%) unless otherwise indicated.
P values less than 0.05 were highlighted in bold.
B+I = bevacizumab + irinotecan combination therapy, BEV = bevacizumab monotherapy, RT = Radiation therapy, TMZ = temozolomide, DM = diabetes mellitus.

These findings suggest that there was no significant difference in survival outcomes between the groups. Kaplan-Meier curves are presented in **Fig. 2**.

Table 2 presents the results of Cox proportional hazards regression analysis with survival time from surgery. In the univariate analysis, the bevacizumab plus irinotecan group did not show a statistically significant hazard ratio (HR) of 1.05 (95% CI, 0.903–1.230; $P = 0.508$), and the prevalence of hypertension was also not significant. However, age, male sex, biopsy, and number of radiotherapy cycles were found to be significantly associated with survival in the univariate analysis. In the multivariate analysis, male sex (HR, 1.28; 95% CI, 1.090–1.496; $P = 0.002$), biopsy (HR, 1.79; 95% CI, 1.334–2.397; $P < 0.0001$), and number of radiotherapy cycles (HR, 0.63; 95% CI, 0.471–0.834; $P = 0.001$) remained the factors that were significantly associated with survival.

Table 3 presents the results of Cox proportional hazards regression analysis with survival time from the initiation of chemotherapy including bevacizumab. In both the univariate and multivariate models, male sex (HR, 1.18; 95% CI, 1.011–1.379; $P = 0.036$) was found to be a significant predictor of poor survival. On the other hand, bevacizumab plus irinotecan, age, and number of radiotherapy cycles did not exhibit a significant association with survival.

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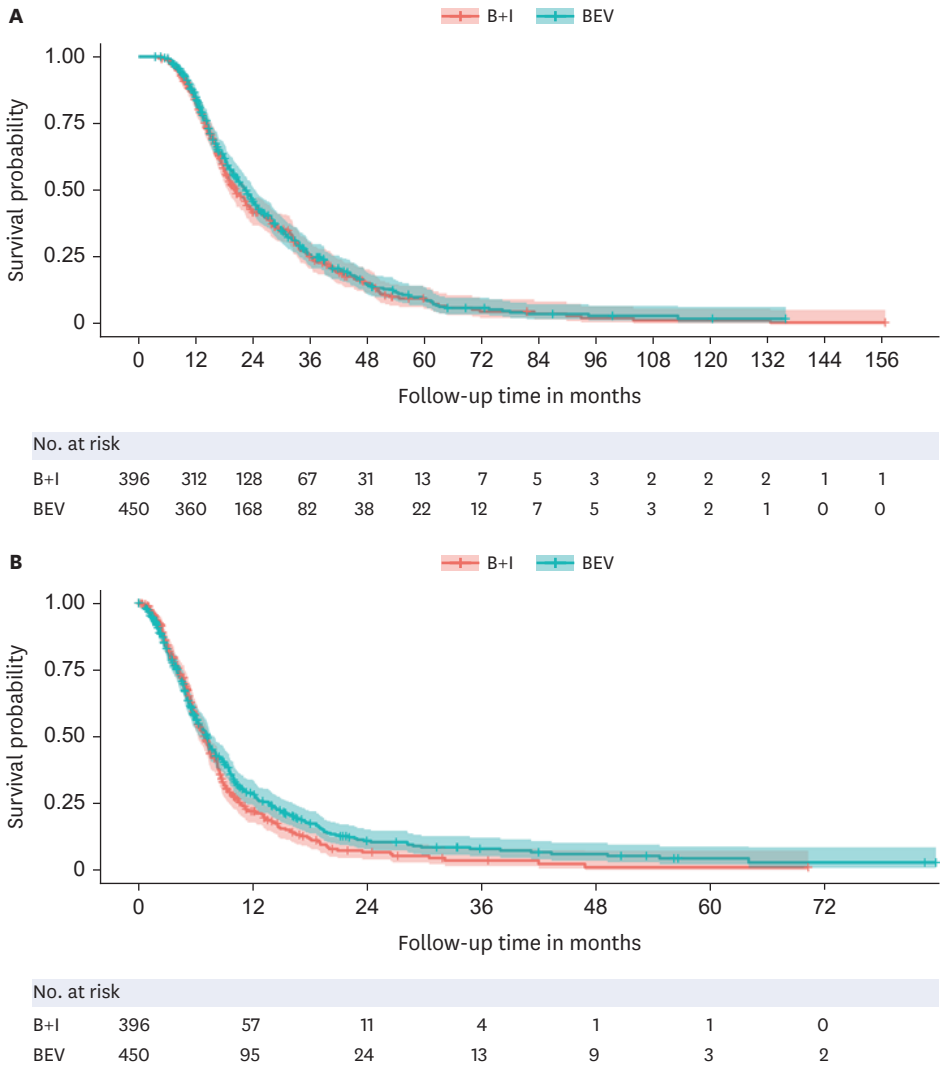

Fig. 2. Survival analysis according to chemotherapy regimen for recurrent glioblastomas. (**A**) Kaplan-Meier curves for survival duration from the time of surgery. (**B**) Kaplan-Meier curves for survival duration from the initiation of chemotherapy including bevacizumab.
BEV = bevacizumab monotherapy, B+I = bevacizumab plus irinotecan combination therapy.

DISCUSSION

This nationwide population-based study aimed to compare the effects of bevacizumab monotherapy versus bevacizumab plus irinotecan combination therapy in patients with recurrent glioblastoma. We utilized a national database to ensure the inclusion of all potential GBM patients, effectively identifying glioblastoma patients through this comprehensive approach. Currently, in the Republic of Korea, bevacizumab plus irinotecan therapy is approved for progressive or recurrent anaplastic astrocytoma or GBM following standard chemoradiation therapy, and for patients under 22 years of age after radiation therapy. Concurrent treatment with temozolomide and radiation is approved only for newly diagnosed glioblastomas, not for anaplastic astrocytoma or other malignant brain tumors. By excluding those who did not receive concurrent chemoradiation treatment, we were able to specifically select patients diagnosed with glioblastoma from those categorized under C71.x.

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Table 2. Cox proportional hazards regression analysis with survival time from surgery

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Group		0.5079		0.395
B+I	1.05 (0.903–1.230)		1.07 (0.915–1.252)	
BEV	Ref.		Ref.	
Age	1.01 (1.000–1.013)	**0.0416**	1.01 (0.999–1.013)	0.089
Sex		**0.0011**		**0.002**
Male	1.30 (1.109–1.514)		1.28 (1.090–1.496)	
Female	Ref.		Ref.	
Type of surgery		< **0.0001**		< **0.0001**
Biopsy	1.82 (1.358–2.429)		1.79 (1.334–2.397)	
Resection	Ref.		Ref.	
HTN		0.0941		0.871
Yes	1.16 (0.976–1.368)		0.98 (0.811–1.194)	
No	Ref.		Ref.	
DM		**0.0261**		0.120
Yes	1.30 (1.032–1.638)		1.22 (0.950–1.568)	
No	Ref.		Ref.	
No. of RT cycle	0.58 (0.438–0.769)	**0.0002**	0.63 (0.471–0.834)	**0.001**

P values less than 0.05 were highlighted in bold.
B+I = bevacizumab + irinotecan combination therapy, BEV = bevacizumab monotherapy, HTN = hypertension, DM = diabetes mellitus, RT = radiation therapy.

Table 3. Cox proportional hazards regression analysis with survival time from the initiation of bevacizumab included chemotherapy

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Group		0.0974		0.121
B+I	1.14 (0.976–1.333)		1.13 (0.968–1.326)	
BEV	Ref.		Ref.	
Age	1.00 (0.994–1.006)	1.0000	1.00 (0.995–1.008)	0.662
Sex		**0.0363**		**0.044**
Male	1.18 (1.011–1.379)		1.18 (1.004–1.379)	
Female	Ref.		Ref.	
Type of surgery		0.3769		0.377
Biopsy	1.14 (0.853–1.521)		1.14 (0.853–1.521)	
Resection	Ref.		Ref.	
HTN		0.8628		0.981
Yes	1.02 (0.858–1.201)		1.00 (0.828–1214)	
No	Ref.		Ref.	
DM		0.8074		0.922
Yes	1.03 (0.817–1.297)		1.01 (0.789–1.300)	
No	Ref.		Ref.	
No. of RT cycle	1.09 (0.825–1.449)	0.5342	1.14 (0.854,1.513)	0.379

P values less than 0.05 were highlighted in bold.
B+I = bevacizumab + irinotecan combination therapy, BEV = bevacizumab monotherapy, HTN = hypertension, DM = diabetes mellitus, RT = radiation therapy.

Our results align with previous findings, reinforcing the robustness of our methodology. According to two studies using data from the Korea Central Cancer Registry, 5,196 patients were diagnosed with glioblastoma from 2007 to 2016.[30,31] Our study identified 8,738 glioblastoma patients over a span of 14 years, which is comparable to the numbers reported in the Korea Central Cancer Registry studies. This similarity underscores the effectiveness and accuracy of our patient selection method.

In terms of demographic characteristics, we found that the bevacizumab group was older and had a higher percentage of women than the bevacizumab plus irinotecan group. This could reflect clinicians' tendency to choose less aggressive treatment options for older

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patients or those with potentially lower physiological reserves. These differences might have impacted the results, because age and sex have been reported to influence the prognosis of patients with glioblastoma. However, after adjusting for age and sex in the multivariate analysis, the treatments were still not significantly associated with survival. We found no significant difference in overall survival between the bevacizumab and bevacizumab plus irinotecan groups. Our results suggest that the addition of irinotecan to bevacizumab does not significantly improve the overall survival in patients with recurrent glioblastoma. Although we were unable to directly verify it in this study, it is worth noting that the patients in the bevacizumab plus irinotecan group were exposed to additional potential side effects including severe diarrhea, nausea, vomiting, neutropenia, liver toxicity, fatigue, and hair loss without gaining a significant survival advantage.[32] This could lead to a decrease in the quality of life and potentially contribute to treatment discontinuation.

In 2008, Friedman et al.[26] conducted a phase II multicenter trial evaluating the efficacy of bevacizumab, both as a monotherapy and in combination with irinotecan, for patients with recurrent glioblastoma. The results indicated that the 6-month progression-free survival rates were 42.6% and 50.3% in the bevacizumab-only and bevacizumab plus irinotecan groups, respectively. The corresponding response rates were 28.2% and 37.8%, and the median overall survival periods were 9.2 and 8.7 months, respectively, in the bevacizumab-only and combination therapy groups. Adverse events were more prominent in the combination therapy group (65.8%) than in the bevacizumab-only group (46.4%). The bevacizumab-only group mainly experienced hypertension (8.3%) and convulsions (6.0%), whereas the combination therapy group reported convulsions (13.9%), neutropenia (8.9%), and fatigue (8.9%). No intergroup difference was statistically significant. While the authors concluded that bevacizumab, both alone and combined with irinotecan, was well-tolerated in the treatment of recurrent glioblastoma, they did not sufficiently elucidate the therapeutic benefits gained from adding irinotecan or safety concerns related to adverse events.

In 2011, Zhang et al.[28] conducted a meta-analysis of patients with recurrent glioblastoma. Among the 480 patients analyzed, 183 and 297 were treated with bevacizumab alone and bevacizumab plus irinotecan, respectively. The corresponding median overall survival periods were 8.63 and 8.91 months. The 6-month progression-free survival rates were 38.8% and 48.3%, respectively, for the bevacizumab and bevacizumab plus irinotecan groups. Notably, a significantly higher rate of discontinuation was observed in the bevacizumab plus irinotecan group (20.0%) than in the bevacizumab group (5.5%). Despite the combination treatment affording a higher progression-free survival rate, the intergroup difference was not significant. Consequently, while the combination treatment may lead to higher discontinuation rates, it did not evidently increase the overall or progression-free survival.

Thus far, large-scale prospective studies comparing bevacizumab monotherapy and bevacizumab plus irinotecan combination therapy on a 1:1 basis are lacking. Even in terms of retrospective studies, no nationwide study with as many subjects as those in our study has been reported. HIRA is a comprehensive and nationally representative database that includes information on patient demographics, diagnoses, treatments, and medical costs for nearly the entire population of South Korea. The data therein are collected from healthcare providers and insurance claims and linked using unique patient identifiers, thereby ensuring the accuracy and consistency of the data. HIRA data are particularly beneficial for medical research as the database provides a large sample size, longitudinal data, and a wide range of variables for analysis.[33,34] In our study, we utilized the comprehensive nature of the HIRA

data, which helped us gather data on the entire South Korean population. This approach also provided insights into bevacizumab administration patterns in patients with recurrent glioblastoma, such as the prevalence and demographics associated with monotherapy versus combination therapy with irinotecan. Therefore, our study could serve as a crucial reference in determining future treatment strategies with bevacizumab. The extensive coverage and large sample size of this study enhance its robustness and generalizability, making it a significant contribution to the field of recurrent glioblastoma treatment. Considering the similar efficacy and the potential for additional toxicity, our study provides valuable evidence for guiding clinical decision-making and suggests that bevacizumab monotherapy may be a preferable option for some patients.

There are several limitations to our study. First, due to its retrospective nature, there may have been unmeasured confounding factors that could have affected the results. Second, we did not have information on molecular markers such as O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status and isocitrate dehydrogenase (IDH) mutation, which are known to influence the prognosis of patients with glioblastoma. According to the most recent WHO diagnostic criteria, IDH mutant tumors are no longer classified as glioblastoma. It is not feasible to extract only IDH wild-type patients from the database, which is a limitation of our study.

Considering patients diagnosed before the introduction of molecular diagnostic criteria, there is a possibility that patients histologically identified as glioblastoma but molecularly as anaplastic astrocytoma or oligodendroglioma might be included, according to the 2021 WHO CNS Classification 5th Edition. However, it is unlikely that the IDH mutation status significantly influenced the decision to include irinotecan in bevacizumab treatment. Additionally, IDH-mutant cases are relatively less likely to relapse, reducing the need for bevacizumab compared to GBM. Therefore, the inclusion of IDH-mutant cases is unlikely to have had a significant impact on the study results.

Bevacizumab monotherapy can be administered for radiation necrosis; therefore, it was necessary to exclude these cases from our analysis. To achieve this, we searched the database for the ICD-10 code G93.81 (radiation necrosis) but found no records. Although G93.81 is the most appropriate code for radiation necrosis, we considered the possibility that radiation necrosis might have been coded using the upper-level code G93.8 (Other specified disorders of brain). Our search revealed that 22 out of 450 patients in the bevacizumab monotherapy group and 19 out of 396 patients in the bevacizumab plus irinotecan group were assigned this code. Given that bevacizumab plus irinotecan is not indicated for radiation necrosis, it appears that the code G93.8 does not accurately reflect cases of radiation necrosis. Even if G93.8 includes cases of radiation necrosis, the relatively small and comparable numbers in both groups suggest that their impact on the overall study outcomes is likely minimal.

Distinguishing between radiation necrosis and recurrence in glioblastoma is notoriously challenging, as lesions initially appearing as radiation necrosis are often later confirmed as recurrences, and vice versa. Even when radiation necrosis is suspected, it is often not confirmed with sufficient certainty to warrant assigning a specific code. This may account for the absence of the G93.81 diagnostic code. This limitation highlights one of the inherent challenges in our study using the HIRA database.

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We did not have detailed data on the performance status and quality of life of patients, which are important factors in evaluating the effectiveness of cancer treatment. Due to the nature of claims databases, the side effects of chemotherapy, Karnofsky Performance Status, or detailed radiographic tumor characteristics could not be assessed. These limitations represent additional challenges in our study. However, we included the length of stay as a variable in our analysis, assuming that patients with poorer performance status would have longer hospitalizations.

In conclusion, our study, utilizing a large-scale national database, reaffirmed that there is no significant difference in overall survival between bevacizumab monotherapy and bevacizumab plus irinotecan combination therapy in patients with recurrent glioblastoma. Considering the additional potential toxicity associated with irinotecan, bevacizumab monotherapy could be a suitable treatment option for patients with recurrent glioblastoma. To further substantiate these findings, additional prospective randomized trials are necessary.

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The figure used in the Graphical Abstract of this paper was created using image sources from BioRender.com.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Code for claims used in database search

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