ANTICANCER RESEARCH *39*: 5733-5739 (2019)
doi:10.21873/anticanres.13774

Patterns of Care After Surgery for Elderly Patients With Malignant Brain Tumors: Data from the National Health Insurance Service in South Korea

HYEON KANG KOH[1,2], HYEONGSU KIM[2,3] and SEMIE HONG[1,2]

[1]*Department of Radiation Oncology, Konkuk University School of Medicine and Konkuk University Medical Center, Seoul, Republic of Korea;*
[2]*Research Institute of Medical Science, Konkuk University School of Medicine, Seoul, Republic of Korea;*
[3]*Department of Preventive Medicine, Konkuk University School of Medicine, Seoul, Republic of Korea*

Abstract. *Background/Aim: To analyze patterns of care and overall survival for elderly patients with malignant brain tumors. Materials and Methods: The database from the National Health Insurance Service was searched January 2008-December 2016. A total of 1,607 patients aged 65-year-old or more with malignant brain tumors who underwent surgery or biopsy were extracted. Treatment performed in 180 days after surgery was divided into no treatment (N=522), radiotherapy (RT) (N=351), chemotherapy (N=69), and chemotherapy plus RT (N=665). Survival was recorded at 3, 6, 9, 12, 18, and 24 months after surgery. Results: Patients were divided into groups by age: 65-69, 70-74, 75-79, and ≥80 years. Chemotherapy plus RT was most commonly used in all age groups except those aged 80 years and more. Treatment modality after surgery or biopsy was significantly prognostic (p<0.001) in univariate analysis. Conclusion: Adjuvant treatment can be recommended for elderly patients with malignant brain tumors based on data from the National Health Insurance Service.*

Malignant brain tumors are rare malignancies and confer poor prognosis (1, 2). In the Surveillance, Epidemiology, and End Results Program Cancer Statistics of the U.S., cancer of the brain and nervous system was 6.4 per 100,000 males and females per year, and caused 4.4 deaths per 100,000 males and females yearly. The associated 5-year survival was 32.9% (1). In Korea in 2016, incidence and death from cancer of the brain and central nervous system is 3.1 and 1.7 per 100,000 males and females per year, respectively. The 5-year survival is approximately 40% (2).

In particular, elderly patients are known to have worse survival prognosis, and are under-represented in clinical trials because of coexisting conditions such as poor overall health status, multiple comorbidities, and polypharmacy (3). Consequently, proper management for elderly patients with malignant brain tumors has been emphasized.

Among malignant brain tumors, glioblastoma (GBM), the most common malignant brain tumor in adults, has been actively studied. Although establishment of standard treatment from the landmark European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada trial consisting of maximal surgical resection followed by concurrent chemoradiotherapy with 60 Gy in 30 fractions of radiotherapy (RT) plus temozolomide, then maintenance therapy of temozolomide, the prognosis of GBM is markedly poor and the median overall survival (OS) of patients is 14.6 months (4). Moreover, patients older than 70 years were excluded from that trial, and fewer than 30% of included patients were older than 60 years (5). Several randomized trials examined elderly patients with GBM. RT was superior in best supportive care (6). Hypofractionated RT of 40 Gy per 15 fractions was compatible with standard RT of 60 Gy per 30 fractions (7). Hypofractionated RT of 34 Gy in 10 fractions or temozolomide alone led to better survival than standard RT in the Nordic trial (8). Dose-dense temozolomide had similar effect to standard RT in a phase III trial of the German Neuro-oncology Working group (9). Recently, 40 Gy of hypofractionated RT plus concurrent temozolomide was found to be superior to hypofractionated RT alone (10). There is no treatment consensus for elderly patients with GBM.

In Korea, all citizens are enrolled in the National Health Insurance Service (NHIS) from birth to death. Thus, administrative claims data are recorded for all citizens. The

Correspondence to: Semie Hong, MD, Department of Radiation Oncology, Konkuk University School of Medicine and Konkuk University Medical Center, 120-1 Neungdong-ro, Gwangjin-gu, Seoul, 05030, Republic of Korea. E-mail: semiehong@kuh.ac.kr

Key Words: Malignant brain tumor, elderly, radiotherapy, national health insurance service.

purpose of this study was to evaluate patterns of care after surgery or biopsy, and OS by treatment modality for elderly patients with malignant brain tumors using data from the NHIS in Korea.

Patients and Methods

Study data and populations. The database system of the NHIS in Korea was retrospectively accessed and administrative claims databases were extracted. We included patients with diagnosis of malignant neoplasm of the brain, unspecified, by International Classification of Diseases, Tenth Revision [ICD-10] code, C719, (11) because we found that several institutions code GBM as C719 even though other malignant tumors may also be included in this code. Patient data were collected from between January 1, 2008 and December 31, 2016 because temozolomide was covered by the NHIS from mid-2007. Elderly patients were defined as those aged 65 years and older. To obtain concise diagnostic information, codes of surgical procedures were included patients. Data for patients who had craniotomy for tumor removal (S4634-7) or stereotactic biopsy (S4756) were extracted.

Treatments and survival outcomes. Treatments within 180 days after surgery were considered. RT data were extracted through codes of HD051-9 (external beam RT), HD061 (three-dimensional conformal RT), HD110-5 (stereotactic radiosurgery), HD121 (proton therapy), and HZ271 (intensity-modulated RT). Chemotherapy was defined as codes of 358201-5ACH for temozolomide because temozolomide was the most commonly used drug for malignant brain tumors. Treatments after surgery were categorized as no treatment, RT alone, chemotherapy alone, and combined treatment with chemotherapy plus RT. Survival data were extracted at 3, 6, 9, 12, 18, and 24 months after surgery.

Statistical analysis. All data are presented as absolute numbers or percentages for each age group. The Kaplan–Meier method was used to calculate actuarial rates of OS up to 24 months. For comparison between groups, two-sided log-rank tests were performed. All tests were bilateral and statistical significance was defined as a p-value of less than 0.05. All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

Ethical statement. This study was approved by the Institutional Review Board of Konkuk University Medical Center (approval No. KUH1280129). Waivers of the requirement for individual informed consent were obtained because this study used secondary data of the NHIS.

Results

Population. A flow diagram for patient selection is presented in Figure 1. From 2008 to 2016, a total of 10,973 patients were diagnosed with an unspecified malignant neoplasm of the brain. Among these patients, there were 2,534 patients aged 65 years or more. Finally, a total of 1,607 patients who underwent surgical procedures remained. These patients were classified onto four groups based on treatment within 180 days after surgery. Gender and age distribution are summarized in Table I. There were 791 female patients and 861 male patients. Patients were divided by age into four groups. There were 645, 542, 290, and 130 patients aged 65-69, 70-74, 75-79, and age ≥80 years, respectively.

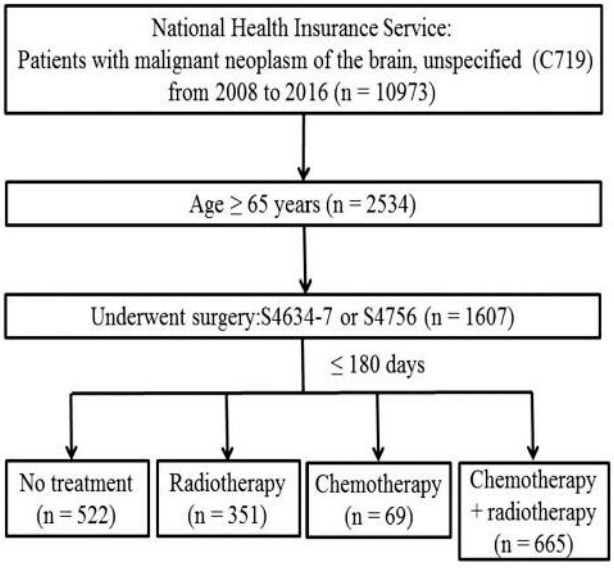

Figure 1. *Patient selection diagram.*

Patterns of care after surgery. Trends of treatment after surgery 2008-2016 are summarized as histograms in Figure 2. Chemotherapy plus RT was most commonly performed, and was used for almost half of the patients. Approximately 30% of patients had no treatment at all. RT alone was conducted for approximately 20% of patients. Chemotherapy alone was performed for approximately 5% of patients. This treatment pattern was followed in age groups 65-79 years (Figure 3A-C). However, patients aged 80 years and older most commonly received no treatment (Figure 3D).

Survival outcomes. Survival data from each patient were extracted up to 24 months. Actuarial 12-month OS for patients with no treatment, treated with RT alone, chemotherapy alone, and chemotherapy plus RT was 50.0%, 66.4%, 63.8%, and 69.3%, respectively (Figure 4). Corresponding actuarial 24-month OS was 42.3%, 45.6%, 39.1%, and 46.2% (Figure 4). On univariate analysis, treatment modality after surgery was a significant prognostic factor for OS ($p<0.001$). When each treatment was compared the other, no treatment was significantly inferior to RT alone ($p=0.006$) and chemotherapy plus RT ($p<0.001$). Other combinations were not significant. In subgroup analysis with patients aged 65-69 years, treatment modality did not affect OS ($p=0.106$, Figure 5A). Actuarial 12-month OS was

Table I. *Gender and age distribution of patients diagnosed with malignant neoplasms of brain, unspecified, after surgery by years.*

	Year of diagnosis, n								
	2008	2009	2010	2011	2012	2013	2014	2015	2016
Gender									
Female	75	73	80	81	85	87	87	105	118
Male	68	80	83	72	101	92	114	84	122
Age, years									
65-69	76	69	66	62	70	71	78	65	88
70-74	44	49	56	54	66	67	65	61	80
75-79	14	29	26	25	34	29	40	44	49
≥80	9	6	15	12	16	12	18	19	23
Total	143	153	163	153	186	179	201	189	240

59.8% for those without treatment, 72.4% for those treated with RT alone, 59.1% for those treated with chemotherapy alone, and 75.3% for those treated with chemotherapy plus RT (Figure 5A). For patients aged 70-74 years, OS was significantly different by treatment modality (p=0.004, Figure 5B). Actuarial 12–month OS was 43.5%, 66.2%, 68.0%, and 66.4%, respectively (Figure 5B). In the remaining age groups, treatment modality was not a significant risk factor (p=0.817 for those aged 75-79 years, and p=0.275 for those aged ≥80 years; Figure 5C and D). Corresponding actuarial 12–month OS of patients aged 75-79 and ≥80 years was 44.3% and 48.4% for those without treatment, 56.9% and 63.0% for those treated with RT alone, 71.4% and 50.0% for those treated with chemotherapy alone, and 57.1% and 69.7% for those treated with chemotherapy plus RT, respectively (Figure 5C and 5D).

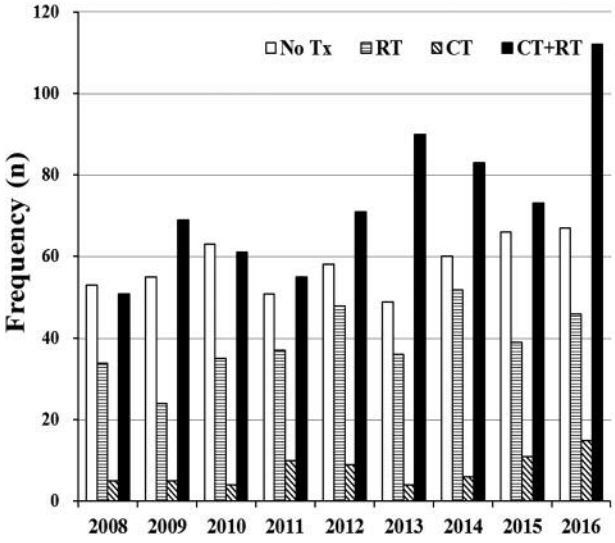

Figure 2. *Patterns of care after surgery in elderly patients with malignant neoplasm, unspecified 2008 through 2016. No Tx: No treatment; RT: radiotherapy; CT: chemotherapy.*

Discussion

In the current study, we investigated patterns of care of elderly patients with malignant brain tumors after surgery or biopsy using data from the NHIS in Korea. Even for elderly patients, chemotherapy plus RT was the most common treatment after surgery or biopsy except for those aged 80 years or older. When we analyzed survival data, treatment modality significantly affected OS (p<0.001). No treatment after surgery or biopsy led to the worst OS.

Optimal treatment for elderly patients with malignant brain tumors has not been determined. As summarized in the introduction, even in GBM, for which standard therapy for young adults has been defined, there was no consensus for treatment of elderly patients (4-10). In this study, chemotherapy plus RT was most commonly used except for patients aged 80 years or more, and led to favorable OS. In a population-based study using the US National Cancer Data Base by Amsbaugh *et al*., chemotherapy plus RT led to the best OS among adjuvant treatments in patients with GBM aged 70 years or more (12). In another study using the US National Cancer Data Base focusing on hypofractionated RT by Haque *et al*., addition of chemotherapy to RT improved OS in patients aged 65 years or more with GBM (13). When adjuvant treatments for GBM in patients aged 65 years and older were compared, hypofractionated RT, standard RT, and chemotherapy alone led to better OS than no adjuvant treatment in another study using the National Cancer Data Base by Bingham *et al*. (14). Even in patients aged 80 years and older, Bracci *et al*. insisted hypofractionated RT

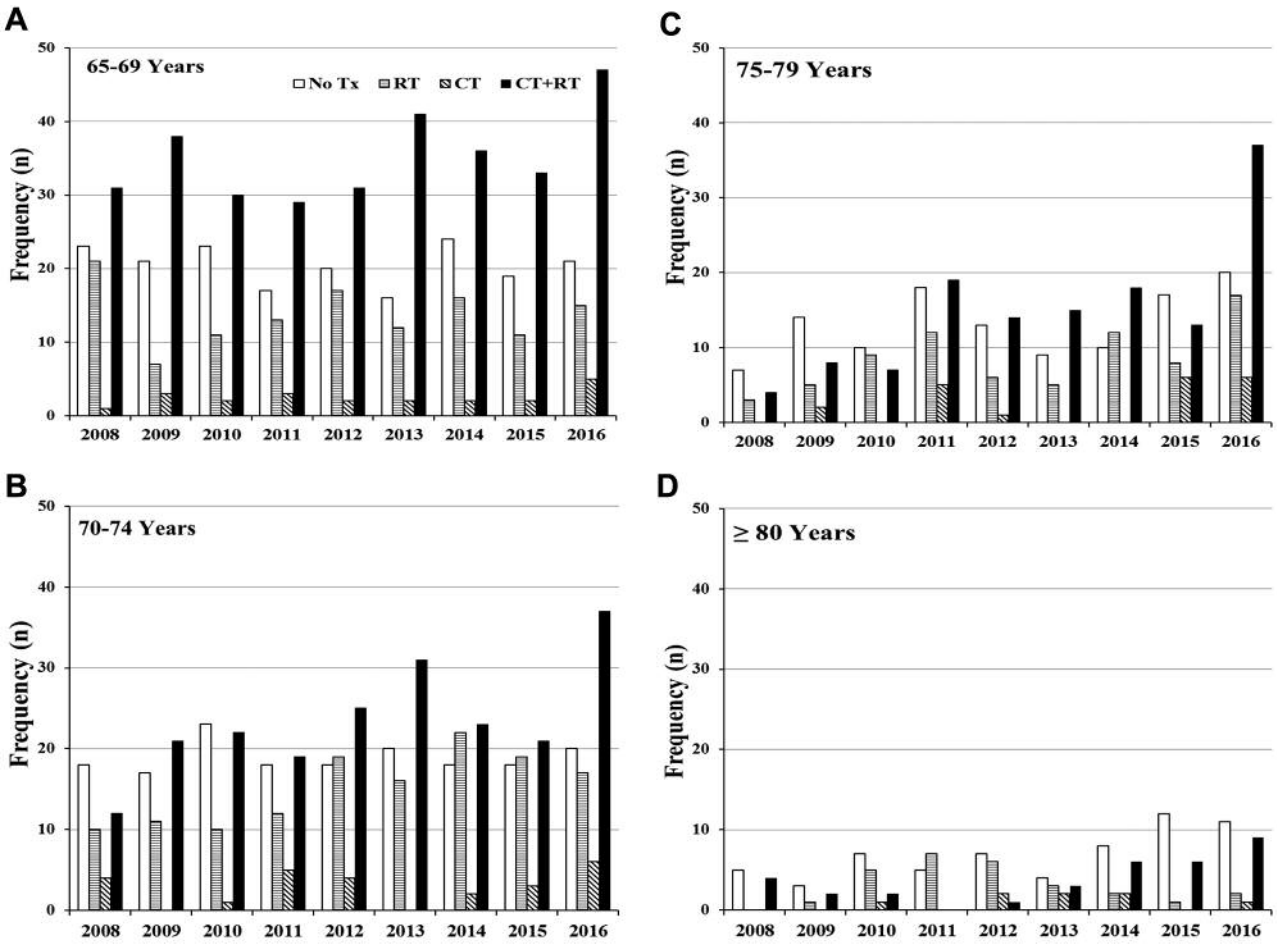

Figure 3. *Patterns of care after surgery by age group 2008 through 2016: A: Age 65-69 years; B: Age 70-74 years; C: Age 75-79 years; D: Age ≥80 years. No Tx: No treatment; RT: radiotherapy; CT: chemotherapy.*

with/without temozolomide was feasible and tolerable in analysis of retrospective data (15). Consequently, based on the present study, adjuvant therapy for malignant brain tumors in elderly patients can be actively considered.

The definition of 'elderly' patients has been variable. The current National Comprehensive Cancer Network guidelines for GBM assesses elderly patients as those older than 70 years (16). In the Korean Society for Neuro-Oncology guideline for GBM, elderly patients were defined as those older than 70 years (17). The European Association for Neuro-Oncology guideline for GBM used 65-70 years as a broad cutoff for dividing patients by age (18). In randomized controlled trials for elderly patients, inclusion criteria for age differed. Keime-Guibert *et al*. enrolled patients aged 70 years and older for comparison of RT with supportive care (6). In a study by Roa *et al*., patients aged 60 years and older were randomized between standard RT and hypofractionated RT

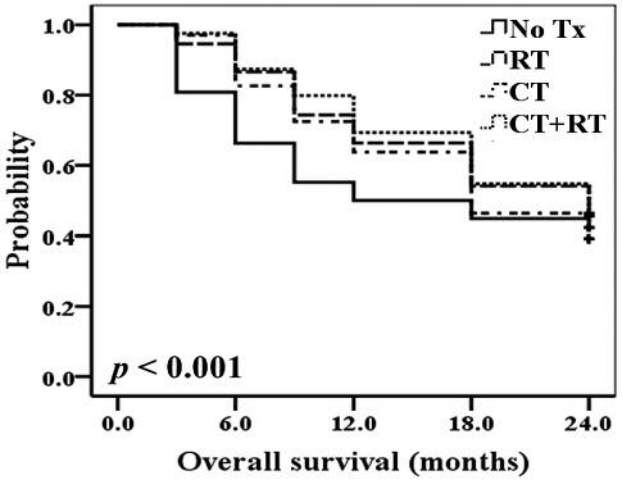

Figure 4. *Overall survival for all patients by treatment modality. No Tx: No treatment; RT: radiotherapy; CT: chemotherapy.*

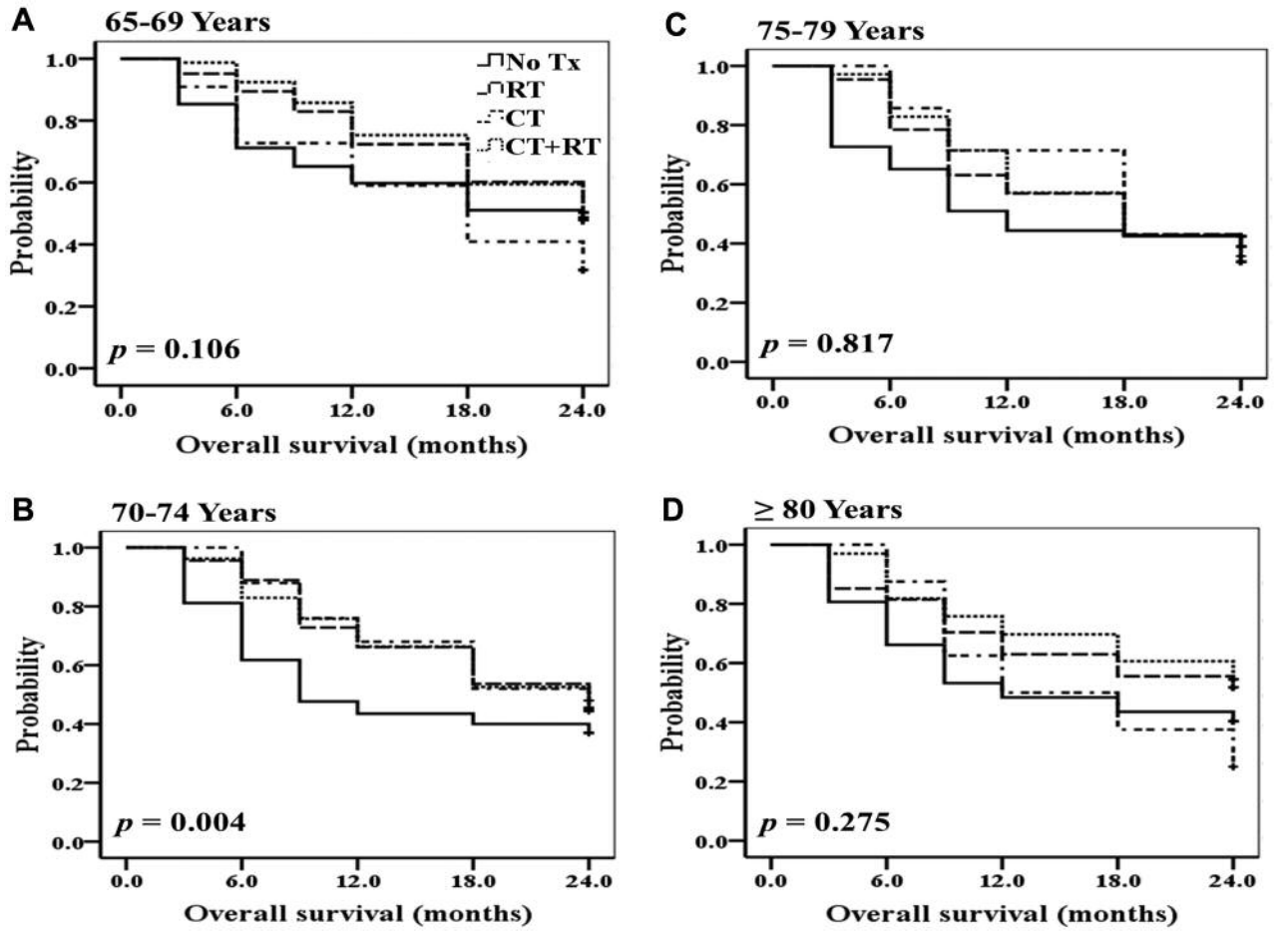

Figure 5. *Overall survival for each age group by treatment modality. A: Age 65-69 years; B: Age 70-74 years; C: Age 75-79 years; D: Age ≥80 years. No Tx: No treatment; RT: radiotherapy; CT: chemotherapy.*

(7). In the Nordic trial, patients aged ≥60 years were included for comparing standard RT, hypofrationated RT, and therapy with temozolomide alone (8). Wick *et al*. defined elderly patients as those older than 65 years in a study to compare standard RT and dose-dense temozolomide (9). Perry *et al*. enrolled patients aged 65 years and older, and randomized hypofractionated RT with/without temozolomide (10). In the present study, we included patients aged 65 years and older. A consistent, standard definition of elderly patients is needed for proper application in daily practice.

In a population-based study using an administrative claims database, proper usage for disease codes is essential. In this study, we sought patients with C719, malignant neoplasm of brain, unspecified, in ICD-10, because several institutions use C719 to code GBM. Nonetheless, other malignant brain tumors as well as GBM were included because actual 24 months OS of patients in the present study was approximately 40%, and much higher than the approximately 10% reported for elderly patients with GBM (6-10). In a previous study in Japan, Yoshimoto *et al*. used code C71 for malignant neoplasm of the brain in ICD-10 to investigate the pattern of treatment for malignant brain tumors, but did not present survival data (19). In another study in the U.S., GBM was found using C71 code in ICD-10 from administrative claims databases. The authors presented patterns of care after surgery and survival graphs with 10-20% OS at 12 months (20).

There are limitations and strengths of the current study. It was not possible to extract data on several risk factors influencing OS in elderly patients, such as the Eastern Cooperative Oncology Group performance status (21), extent of surgery (22), fractionation of RT (7, 8), and molecular status (23) from reimbursement data. Additionally, selection bias could not be excluded due to the retrospective nature of this study. However, we collected a large number of patients receiving relatively consistent treatment and showed survival data based on the universal healthcare system in Korea.

In conclusion, patients aged 65 and older with malignant brain tumors received chemotherapy plus RT most

commonly after surgery or biopsy based on data from the NHIS in Korea. Adjuvant therapy such as RT alone or chemotherapy plus RT were superior to no treatment in univariate analysis, and can be recommended for such patients. Further validation or a plan for phase III trials is needed to confirm population-based data from the reimbursement system.

Conflicts of Interest

There are no conflicts of interest related to this article.

Authors' Contributions

Hyeon Kang Koh: Conception/design, interpretation of data, statistical analysis, writing, editing, and approval of the article. Hyeongsu Kim: Collection of data, interpretation of data, statistical analysis, writing, editing, and approval of the article. Semie Hong: Conception/design, interpretation of data, writing, editing, and final approval of the article.

References

1 SEER Cancer Statistics Factsheets: Brain and other nervous system cancer. National Cancer Institute. Bethesda, MD. Available at: https://seer.cancer.gov/statfacts/html/brain.html (last accessed on 2nd August 2019)

2 Jung KW, Won YJ, Kong HJ and Lee ES: Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2016. Cancer Res Treat *51(2)*: 417-430, 2019. PMID: 30913865. DOI: 10.4143/crt.2019.138

3 Nayak L and Iwamoto FM: Primary brain tumors in the elderly. Curr Neurol Neurosci Rep *10(4)*: 252-258, 2010. PMID: 20461477. DOI: 10.1007/s11910-010-0110-x

4 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med *352(10)*: 987-996, 2005. PMID: 15758009. DOI: 10.1056/NEJMoa043330

5 Azrnett OJ, Sahgal A, Gosio J, Perry J, Berger MS, Chang S and Das S: Treatment of elderly patients with glioblastoma: a systematic evidence-based analysis. JAMA Neurol *72(5)*: 589-596, 2015. PMID: 25822375. DOI: 10.1001/jamaneurol.2014.3739

6 Keime-Guibert F, Chinot O, Taillandier L, Cartalat-Carel S, Frenay M, Kantor G, Guillamo JS, Jadaud E, Colin P, Bondiau PY, Meneï P, Loiseau H, Bernier V, Honnorat J, Barrié M, Mokhtari K, Mazeron JJ, Bissery A, Delattre JY; Association of French-Speaking Neuro-Oncologists: Radiotherapy for glioblastoma in the elderly. N Engl J Med *356(15)*: 1527-1535, 2007. PMID: 17429084. DOI: 10.1056/NEJMoa065901

7 Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, Fisher B, Fulton D, Gulavita S, Hao C, Husain S, Murtha A, Petruk K, Stewart D, Tai P, Urtasun R, Cairncross JG and Forsyth P: Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol *22(9)*: 1583-1588, 2004. PMID: 15051755. DOI: 10.1200/JCO.2004.06.082

8 Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, Abacioglu U, Tavelin B, Lhermitte B, Hegi ME, Rosell J, Henriksson R; Nordic Clinical Brain Tumour Study Group (NCBTSG): Temozolomide *versus* standard 6-week radiotherapy *versus* hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol *13(9)*: 916-926, 2012. PMID: 22877848. DOI: 10.1016/S1470-2045(12)70265-6

9 Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, Nikkhah G, Papsdorf K, Steinbach JP, Sabel M, Combs SE, Vesper J, Braun C, Meixensberger J, Ketter R, Mayer-Steinacker R, Reifenberger G, Weller M; NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society: Temozolomide chemotherapy alone *versus* radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol *13(7)*: 707-715, 2012. PMID: 22578793. DOI: 10.1016/S1470-2045(12)70164-X

10 Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, Fay M, Nishikawa R, Cairncross JG, Roa W, Osoba D, Rossiter JP, Sahgal A, Hirte H, Laigle-Donadey F, Franceschi E, Chinot O, Golfinopoulos V, Fariselli L, Wick A, Feuvret L, Back M, Tills M, Winch C, Baumert BG, Wick W, Ding K, Mason WP; Trial Investigators: Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med *376(11)*: 1027-1037, 2017. PMID: 28296618. DOI: 10.1056/NEJMoa1611977

11 World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision, Second Edition. World Health Organization, 2004. Available at: https://apps.who.int/iris/handle/10665/42980 (last accessed on 3rd August 2019)

12 Amsbaugh MJ, Yusuf MB, Gaskins J, Burton EC and Woo SY: Patterns of care and predictors of adjuvant therapies in elderly patients with glioblastoma: An analysis of the National Cancer Data Base. Cancer *123(17)*: 3277-3284, 2017. PMID: 28452053. DOI: 10.1002/cncr.30730

13 Haque W, Verma V, Butler EB and Teh BS: Addition of chemotherapy to hypofractionated radiotherapy for glioblastoma: practice patterns, outcomes, and predictors of survival. J Neurooncol *136(2)*: 307-315, 2018. PMID: 29090416. DOI: 10.1007/s11060-017-2654-y

14 Bingham B, Patel CG, Shinohara ET and Attia A: Utilization of hypofractionated radiotherapy in treatment of glioblastoma multiforme in elderly patients not receiving adjuvant chemoradiotherapy: A National Cancer Database Analysis. J Neurooncol *136(2)*: 385-394, 2018. PMID: 29209874. DOI: 10.1007/s11060-017-2665-8

15 Bracci S, Laigle-Donadey F, Hitchcock K, Duran-Peña A, Navarro S, Chevalier A, Jacob J, Troussier I, Delattre JY, Mazeron JJ, Hoang-Xuan K and Feuvret L: Role of irradiation for patients over 80 years old with glioblastoma: A retrospective cohort study. J Neurooncol *129(2)*: 347-353, 2016. PMID: 27311728. DOI: 10.1007/s11060-016-2182-1

16 National Comprehensive Cancer Network: Central Nervous System Cancers (Version 1. 2019). Available at: https://

www.nccn.org/professionals/physician_gls/pdf/cns.pdf (last accessed on 3rd August 2019)

17 Kim YZ, Kim CY, Lim J, Sung KS, Lee J, Oh HJ, Kang SG, Kang SH, Kong DS, Kim SH, Kim SH, Kim SH, Kim YJ, Kim EH, Kim IA, Kim HS, Roh TH, Park JS, Park HJ, Song SW, Yang SH, Yoon WS, Yoon HI, Lee ST, Lee SW, Lee YS, Wee CW, Chang JH, Jung TY, Jung HL, Cho JH, Choi SH, Choi HS, Hong JB, Lim DH, Chung DS; KSNO Guideline Working Group: The Korean Society for Neuro-Oncology (KSNO) Guideline for Glioblastomas: Version 2018.01. Brain Tumor Res Treat *7(1)*: 1-9, 2019. PMID: 31062525. DOI: 10.14791/btrt.2019.7.e25

18 Weller M, van den Bent M, Hopkins K, Tonn JC, Stupp R, Falini A, Cohen-Jonathan-Moyal E, Frappaz D, Henriksson R, Balana C, Chinot O, Ram Z, Reifenberger G, Soffietti R, Wick W; European Association for Neuro-Oncology (EANO) Task Force on Malignant Glioma: EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol *15(9)*: e395-403, 2014. PMID: 25079102. DOI: 10.1016/S1470-2045(14)70011-7

19 Yoshimoto K, Kada A, Kuga D, Hatae R, Murata H, Akagi Y, Nishimura K, Kurogi R, Nishimura A, Hata N, Mizoguchi M, Sayama T and Iihara K: Current trends and healthcare resource usage in the hospital treatment of primary malignant brain tumor in Japan: A national survey using the diagnostic procedure combination database (J-ASPECT Study-Brain Tumor). Neurol Med Chir *56(11)*: 664-673, 2016. PMID: 27680329. DOI: 10.2176/nmc.oa.2016-0172

20 Norden AD, Korytowsky B, You M, Kim Le T, Dastani H, Bobiak S and Singh P: A real-world claims analysis of costs and patterns of care in treated patients with glioblastoma multiforme in the United States. J Manag Care Spec Pharm *25(4)*: 428-436, 2019. PMID: 30917077. DOI: 10.18553/jmcp.2019.25.4.428

21 Gately L, Collins A, Murphy M and Dowling A: Age alone is not a predictor for survival in glioblastoma. J Neurooncol *129(3)*: 479-485, 2016. PMID: 27406585. DOI: 10.1007/s11060-016-2194-x

22 Heiland DH, Haaker G, Watzlawick R, Delev D, Masalha W, Franco P, Machein M, Staszewski O, Oelhke O, Nicolay NH and Schnell O: One decade of glioblastoma multiforme surgery in 342 elderly patients: What have we learned? J Neurooncol *140(2)*: 385-391, 2018. PMID: 30076585. DOI: 10.1007/s11060-018-2964-8

23 Gerstner ER, Yip S, Wang DL, Louis DN, Iafrate AJ and Batchelor TT: MGMT methylation is a prognostic biomarker in elderly patients with newly diagnosed glioblastoma. Neurology *73(18)*: 1509-1510, 2009. PMID: 19884580. DOI: 10.1212/WNL.0b013e3181bf9907

Received August 16, 2019
Revised September 10, 2019
Accepted September 13, 2019