

The Korean Society for Neuro-Oncology (KSNO) Guideline for the Management of Brain Tumor Patients During the Crisis Period: A Consensus Survey About Specific Clinical Scenarios (Version 2023.1)

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Methods The KSNO Guideline Working Group consisted of 22 multidisciplinary experts on neuro-oncology in Korea. In order to confirm a consensus reached by the experts, opinions on 5 specific clinical scenarios about the management of brain tumor patients during the crisis period were devised and asked. To build-up the consensus process, Delphi method was employed.

Results The summary of the final consensus from each scenario are as follows. For patients with newly diagnosed astrocytoma with isocitrate dehydrogenase (*IDH*)-mutant and oligodendroglioma with *IDH*-mutant/1p19q codeleted, observation was preferred for patients with low-risk, World Health Organization (WHO) grade 2, and Karnofsky Performance Scale (KPS) ≥60, while adjuvant radiotherapy

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alone was preferred for patients with high-risk, WHO grade 2, and KPS \geq 60. For newly diagnosed patients with glioblastoma, the most preferred adjuvant treatment strategy after surgery was radiotherapy plus temozolomide except for patients aged \geq 70 years with KPS of 60 and unmethylated *MGMT* promoters. In patients with symptomatic brain metastasis, the preferred treatment differed according to the number of brain metastasis and performance status. For patients with newly diagnosed atypical meningioma, adjuvant radiation was deferred in patients with older age, poor performance status, complete resection, or low mitotic count.

Conclusion It is imperative that proper medical care for brain tumor patients be sustained and provided, even during the crisis period. The findings of this consensus survey will be a useful reference in determining appropriate treatment options for brain tumor patients in the specific clinical scenarios covered by the survey during the future crisis.

Keywords

s Korean Society for Neuro-Oncology; Crisis; Astrocytoma; Oligodendroglioma; Glioblastoma; Brain metastases; Meningioma; Guideline.

INTRODUCTION

The coronavirus disease (COVID-19) pandemic, which began at the end of 2019, has become a prolonged global event with no prior precedent. The healthcare system faced numerous crises that threatened to overload existing medical systems, leading to a sudden increase in demand for COVID-19 treatments, a shortage of medical resources, and a temporary disruption in the provision of care for patients with other illnesses. Brain tumor patients were not exempt from these difficulties, and healthcare professionals struggled to provide adequate management under these resource-constrained conditions. However, providing effective management for patients in a crisis without proper guidelines can be difficult.

In response to this, the Korean Society for Neuro-Oncology (KSNO), a multidisciplinary academic society, has developed specialized clinical guidelines for brain tumor patient care during a crisis. As part II of the guideline, this consensus survey was conducted to provide appropriate management options in specific clinical situations during the crisis period. The crisis period is defined as a situation in which medical resources for the management of brain tumor patients are restricted because of various causes, such as natural disasters, infectious diseases, and wars, making it impossible to proceed with management as usual. This survey addresses the following five types of brain tumors: newly diagnosed astrocytoma with isocitrate dehydrogenase (IDH)-mutant type, newly diagnosed oligodendroglioma with both IDH-mutant and 1p19q co-deletion, newly diagnosed glioblastoma, newly developed symptomatic brain metastases, and newly diagnosed atypical meningioma.

METHODS

The details of the survey design, outline, and implementation are described in the previous article of the series in this issue. In the current consensus survey, we investigated appropriate management options in five specific clinical scenarios during the crisis period. Scenario 1 was designed to evaluate the appropriate management option considering Karnofsky Performance Scale (KPS) and risk in the newly diagnosed astrocytoma with IDH-mutant type during the crisis period. Scenario 2 was a survey about the appropriate treatment strategy considering KPS and risk in the newly diagnosed oligodendroglioma with both IDH-mutant and 1p19q co-deletion during the crisis period. Scenario 3 aimed to investigate appropriate adjuvant treatment and radiotherapy schedules considering age, KPS, the extent of resection, and methylation status of the O^6 -methylguanine-DNA methyltransferase (MGMT) promoter in the newly diagnosed glioblastoma during the crisis period. Scenario 4 aimed to select an appropriate radiotherapy strategy considering KPS and the number of brain metastases in newly developed symptomatic brain metastases during the crisis period. Lastly, Scenario 5 concerned appropriate adjuvant management and radiotherapy schedule in the newly diagnosed atypical meningioma during the crisis period. All questionnaires regarding the five clinical scenarios are presented in the Supplementary Material (in the online-only Data Supplement).

RESULTS

Newly diagnosed astrocytoma, IDH-mutant

For patients with World Health Organization (WHO) grade 2, KPS \geq 60, and low risk, the majority of responses (85.7%) favored observation. For patients with WHO grade 2, KPS \geq 60, and high risk, radiotherapy alone was the preferred treatment for 81% of responses, while radiotherapy with adjuvant PCV (procarbazine, lomustine, and vincristine) or radiotherapy with concurrent and adjuvant temozolomide (TMZ) each were preferred by 4.8%. For patients with WHO grade 3 or 4

and KPS \geq 60, radiotherapy with concurrent and adjuvant TMZ was the most favored treatment, with 42.9% of responses. Radiotherapy with adjuvant TMZ was the second most favored with 38.1% of responses, followed by radiotherapy with adjuvant PCV with 14.3% of responses. For patients with KPS <60 regardless of WHO grade, best supportive care alone was favored by 66.7% of responses. Table 1 shows the summary of responses regarding treatment for patients newly diagnosed with astrocytoma, *IDH*-mutant during the crisis period.

Newly diagnosed oligodendroglioma, *IDH*-mutant and 1p19q codeleted

For patients with WHO grade 2 and KPS \geq 60, the majority (90.5%) chose observation as the best treatment strategy in lowrisk cases, while radiotherapy was selected by 9.5%. In high-risk cases, the majority (57.1%) chose radiotherapy alone, while 23.8% chose radiotherapy with adjuvant PCV, 4.8% chose radiotherapy with concurrent and adjuvant TMZ, and only 14.3% chose observation. For patients with WHO grade 3 and KPS \geq 60, the majority (81%) chose radiotherapy with adjuvant TMZ,

Table 1. Summary of responses regarding treatment for patientsnewly diagnosed with astrocytoma, *IDH*-mutant during the crisisperiod

Question: which treatment strategy is best	Response
in the following situations?	n (%)
(A) WHO grade 2, KPS \geq 60, and low risk*	
Observation	18 (85.7)
Radiotherapy	3 (14.3)
(B) WHO grade 2, KPS \geq 60, and high risk [†]	
Observation	2 (9.5)
Radiotherapy	17 (81.0)
Radiotherapy + adjuvant PCV	1 (4.8)
Radiotherapy + adjuvant TMZ	0 (0)
Radiotherapy with concurrent TMZ + adjuvant TMZ	1 (4.8)
(C) WHO grade 3 or 4 and KPS ≥ 60	
Observation	1 (4.8)
Radiotherapy + adjuvant PCV	3 (14.3)
Radiotherapy + adjuvant TMZ	8 (38.1)
Radiotherapy with concurrent TMZ + adjuvant TMZ	9 (42.9)
(D) KPS <60 regardless of WHO grade	
Best supportive care alone	14 (66.7)
Radiotherapy	3 (14.3)
Radiotherapy with concurrent TMZ	1 (4.8)
Radiotherapy + adjuvant TMZ	1 (4.8)
TMZ alone	2 (9.5)

*Low risk: ≤40 years old and gross total resection; [†]High risk: >40 years old or subtotal resection or open/stereotactic biopsy. WHO, World Health Organization; KPS, Karnofsky Performance Scale; PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide

4.8% chose radiotherapy with concurrent and adjuvant TMZ, and only 4.8% chose observation. For patients with KPS <60 regardless of WHO grade, the majority (71.4%) chose best supportive care alone, 14.3% chose radiotherapy alone, 4.8% chose radiotherapy with concurrent TMZ, 4.8% chose radiotherapy with adjuvant TMZ, and only 4.8% chose TMZ alone. The summary of responses regarding treatment for patients newly diagnosed with oligodendroglioma and *IDH*-mutant 1p19q codeleted is presented in Table 2.

Newly diagnosed glioblastoma

Sixteen potential clinical scenarios of newly diagnosed glioblastoma based on age (64 vs. 76 years), KPS (90 vs. 60 points), extent of resection (gross total resection vs. partial resection), and methylation status of the *MGMT* promoter (methylated vs. unmethylated) were created. Expert panels were required to answer the most appropriate adjuvant treatment combination (best supportive care, radiotherapy alone, radiotherapy plus TMZ, or TMZ alone) and radiotherapy dose-fractionation (60 Gy in 30 fractions, 40 Gy in 15 fractions, 34 Gy in 10 fractions, or 25 Gy in 5 fractions) during the crisis period with

 Table 2. Summary of responses regarding treatment for patients newly diagnosed with oligodendroglioma, *IDH*-mutant and 1p19q codeleted during the crisis period

Question: which treatment strategy is best	Response		
in the following situations?	n (%)		
(A) WHO grade 2, KPS \geq 60, and low risk*			
Observation	19 (90.5)		
Radiotherapy	2 (9.5)		
(B) WHO grade 2, KPS \geq 60, and high risk [†]			
Observation	3 (14.3)		
Radiotherapy	12 (57.1)		
Radiotherapy + adjuvant PCV	5 (23.8)		
Radiotherapy + adjuvant TMZ	0 (0)		
Radiotherapy with concurrent TMZ + adjuvant TMZ	2 1 (4.8)		
(C) WHO grade 3 and KPS ≥60			
Observation	1 (4.8)		
Radiotherapy + neoadjuvant or adjuvant PCV	17 (81.0)		
Radiotherapy + adjuvant TMZ	2 (9.5)		
Radiotherapy with concurrent TMZ + adjuvant TMZ 1 (4.8)			
(D) KPS <60 regardless of WHO grade			
Best supportive care alone	15 (71.4)		
Radiotherapy	3 (14.3)		
Radiotherapy with concurrent TMZ	1 (4.8)		
Radiotherapy + adjuvant TMZ	1 (4.8)		
TMZ alone	1 (4.8)		

*Low risk: ≤40 years old and gross total resection; †High risk: >40 years old or subtotal resection or open/stereotactic biopsy. WHO, World Health Organization; KPS, Karnofsky Performance Scale; PCV, procarbazine, lomustine, and vincristine; TMZ, temozolomide

Table 3. Most frequently answered adjuvant treatment and radiotherapy dose-fractionation schedule per case-scenario in newly diagnosed
glioblastoma during the crisis period

Age/KPS	Treatment -	GTR		PR	
Age/NP3		MGMTp: methylated	<i>MGMT</i> p: unmethylated	<i>MGMT</i> p: methylated	MGMTp: unmethylated
Age: 64/KPS: 90	Adjuvant therapy	RT plus TMZ (100.0%)	RT plus TMZ (76.2%)	RT plus TMZ (95.2%)	RT plus TMZ (71.4%)
	RT schedule	60 Gy/30 fx (66.7%)	60 Gy/30 fx (66.7%)	60 Gy/30 fx (65.0%)	60 Gy/30 fx (55.0%)
Age: 76/KPS: 90	Adjuvant therapy	RT plus TMZ (95.2%)	RT plus TMZ (61.9%)	RT plus TMZ (90.5%)	RT plus TMZ (61.9%)
	RT schedule	40 Gy/15 fx (85.0%)	40 Gy/15 fx (80.0%)	40 Gy/15 fx (78.9%)	40 Gy/15 fx (75.0%)
Age: 64/KPS: 60	Adjuvant therapy	RT plus TMZ (81.0%)	RT plus TMZ (57.1%)	RT plus TMZ (81.0%)	RT plus TMZ (61.9%)
	RT schedule	40 Gy/15 fx (58.8%)	40 Gy/15 fx (55.6%)	40 Gy/15 fx (52.9%)	40 Gy/15 fx (52.9%)
Age: 76/KPS: 60	Adjuvant therapy	RT plus TMZ (61.9%)	RT alone (52.4%)	RT plus TMZ (57.1%)	RT alone (52.4%)
	RT schedule	40 Gy/15 fx (80.0%)	40 Gy/15 fx (80.0%)	40 Gy/15 fx (71.4%)	40 Gy/15 fx (71.4%)

KPS, Karnofsky Performance Scale; GTR, gross total resection; PR, partial resection; *MGMT*p, O⁶-methylguanine-DNA methyltransferase promotor; RT, radiotherapy; TMZ, temozolomide; fx, fractions

 Table 4. Most frequently answered radiotherapy strategy per case-scenario in newly developed symptomatic brain metastasis during the crisis period

KPS	Treatment	Number of BM: 3	Number of BM: 10
KPS: 70	RT type	Radiosurgery (95.2%)	WBRT (76.2%)
	If WBRT	N/A	30 Gy/10 fx (66.6%)
KPS: 40	RT type	Radiosurgery (76.2%)	BSC (61.9%)
	If WBRT	N/A	20 Gy/5 fx (80.0%)

KPS, Karnofsky Performance Scale; BM, brain metastases; RT, radiotherapy; WBRT, whole brain radiotherapy; BSC, best supportive care; N/A, not available; fx, fractions

shortage of healthcare resource.

The most frequently answered treatment combination and radiotherapy dose per scenario is summarized in Table 3. Combination of radiotherapy plus TMZ was the preferred adjuvant treatment method in almost all case-scenarios (87.5%, 14/16). Radiotherapy alone was the preferred regimen only in patients aged 76 years with KPS of 60 points and unmethylated *MGMT* promoters. Interestingly, in no case-scenario was TMZ alone the preferred adjuvant treatment combination. In patients aged 64 years with KPS of 90 points, 60 Gy in 30 fractions was the most preferred radiotherapy regimen despite the shortage of resources during the crisis period. However, besides those patients, 40 Gy in 15 fractions was the most preferred regimen.

Newly diagnosed symptomatic brain metastases

Based on performance status (KPS 70 vs. 40) and number of brain metastases (3 vs. 10), four case-scenarios were developed, and expert panels answered the survey on the most appropriate radiotherapy type (radiosurgery, whole brain radiotherapy, or best supportive care) and whole brain radiotherapy dose-fractionation during the crisis period for each case (Table 4). For patients with 3 brain metastases, no panel recommended whole brain radiotherapy during the crisis period. In contrast, in patients with 10 brain metastases, whole brain radiotherapy (76.2%) and best supportive care (61.9%) was the preferred treatment in patients with KPS 70 and KPS 40, respectively. Despite the shortage of medical resources, the most preferred whole brain radiotherapy regimen was 30 Gy in 10 fractions (66.6%) over 20 Gy in 5 fractions (33.3%) in patients with 10 brain metastases and KPS of 70.

Newly diagnosed atypical meningioma

Similarly, based on age (57 vs. 82 years), KPS (90 vs. 60), extent of resection (gross total resection vs. subtotal/partial resection), and mitotic count, 16 clinical scenarios were proposed for patients with newly diagnosed atypical meningioma. The optimal adjuvant treatment (surveillance, conventional radiotherapy, or radiosurgery) and radiotherapy dose-fractionation (60 Gy in 30 fractions, 54 Gy in 30 fractions, or other) in case of conventional radiotherapy during the crisis period were surveyed (Table 5). For 82-year-old patients who underwent gross total resection, surveillance was the most preferred treatment regardless of mitotic count or KPS. In case of conventional radiotherapy, 54 Gy in 30 fractions was the most preferred regimen in most scenarios (Table 5).

DISCUSSION

Newly diagnosed astrocytoma, *IDH*-mutant and oligodendroglioma, *IDH*-mutant and 1p19q codeleted

The majority of the panel agreed that a more conservative approach to treatment is suitable for patients newly diagnosed with WHO grade 2 astrocytoma and oligodendroglioma during the crisis period. The EORTC 22845 trial demonstrated that early radiotherapy after surgery improved progressionfree survival by two years compared to deferred radiotherapy until progression in patients with low-grade astrocytoma and oligodendroglioma with KPS \geq 60, but did not affect overall survival [1]. The panel mostly agreed that this conservative strategy should be maintained for patients with low-risk *IDH*-

Age/KPS	Treatment	GTR		STR/PR	
Age/NP3		Mitosis: 4	Mitosis: 15	Mitosis: 4	Mitosis: 15
Age: 57/KPS: 90	Adjuvant therapy	Surveillance (81.0%)	Conventional RT	Conventional RT	Conventional RT (81.0%)
			(61.9%)	(61.9%)	
	If conventional RT	54 Gy/30 fx (60.0%)	54 Gy/30 fx (57.1%)	54 Gy/30 fx (50.0%)	60 Gy/30 fx (66.7%)
Age: 82/KPS: 90	Adjuvant therapy	Surveillance (90.5%)	Surveillance (66.7%)	Radiosurgery (47.6%)	Conventional RT (57.1%)
	If conventional RT	54 Gy/30 fx (50.0%)	54 Gy/30 fx (57.1%)	54 Gy/30 fx (50.0%)	54 Gy/30 fx (53.8%)
Age: 57/KPS: 60	Adjuvant therapy	Surveillance (81.0%)	Surveillance (61.9%)	Radiosurgery (52.4%)	Conventional RT (66.7%)
	If conventional RT	54 Gy/30 fx (80.0%)	54 Gy/30 fx (71.4%)	54 Gy/30 fx (54.5%)	54 Gy/30 fx (53.3%)
Age: 82/KPS: 60	Adjuvant therapy	Surveillance (90.5%)	Surveillance (71.4%)	Surveillance (42.9%)	Surveillance (38.1%)
	If conventional RT	54 Gy/30 fx (50.0%)	54 Gy/30 fx (50.0%)	60 Gy/30 fx (50.0%)	54 Gy/30 fx (50.0%)
0	If conventional RT Adjuvant therapy	54 Gy/30 fx (80.0%) Surveillance (90.5%)	54 Gy/30 fx (71.4%) Surveillance (71.4%)	54 Gy/30 fx (54.5%) Surveillance (42.9%)	54 Gy/30 fx (53.3%) Surveillance (38.1%)

Table 5. Most frequently answered adjuvant treatment and radiotherapy dose-fractionation schedule per case-scenario in newly diagnosed atypical meningioma during the crisis period

KPS, Karnofsky Performance Scale; GTR, gross total resection; STR, subtotal resection; PR, partial resection; RT, radiotherapy; fx, fractions

mutant astrocytoma and low-risk IDH-mutant, 1p19q codeleted oligodendroglioma during the crisis period. However, in cases of WHO grade 2 astrocytoma and oligodendroglioma with high risk, particularly those with IDH mutations, radiotherapy with adjuvant PCV was found to have superior progression-free and overall survival compared to radiotherapy alone after surgery [2]. For these high-risk patients, the National Comprehensive Cancer Network (NCCN) guideline suggests using radiotherapy with adjuvant PCV as a category 1 recommendation during non-crisis periods [3]. Nevertheless, the panel did not believe that the addition of adjuvant PCV would have the same degree of benefit during the crisis period. The PCV regimen has a more toxic profile and requires more frequent hospital visits for intravenous vincristine administration and a multiple-dose oral medication schedule [4,5]. The panel expressed concern that the chemotherapy schedule and management of its adverse effects may be impacted by the crisis situation.

The panel had varying preferences for postoperative treatment strategies between patients with grade 3 oligodendroglioma, IDH-mutant/1p19q codeleted and grade 3 or 4 astrocytoma, *IDH*-mutant who have KPS \geq 60. For patients with grade 3 oligodendroglioma, IDH-mutant/1p19q codeleted, the panel strongly recommended radiotherapy with adjuvant PCV, which is suggested as a preferred option in the national guidelines in the non-crisis period [3,6]. This recommendation is based on the findings of RTOG 9402 and EORTC 26951 trials, which demonstrate the substantial improvement in overall survival for patients with 1p19q codeleted oligodendroglioma who receive radiotherapy with adjuvant PCV compared to those who receive adjuvant radiotherapy alone [4,7]. With a median overall survival of 14.7 years and a nearly 50% reduced risk of death, respectively, these results provide strong evidence for the superiority of radiotherapy with adjuvant PCV over adjuvant radiotherapy alone. Even during the crisis period, which tends to favor more conservative treatment strategy, the panel agreed that the remarkable survival benefit seen with radiotherapy with adjuvant PCV justifies its use in these patients. Although the CODEL trial which compare radiotherapy with adjuvant PCV to radiotherapy with concurrent and adjuvant TMZ for grade 3 oligodendroglioma is ongoing, its result is still immature [8]. In contrast, the panel did not favor radiotherapy with adjuvant PCV as the postoperative treatment strategy for patients with grade 3 or 4 astrocytoma, IDHmutant. A large retrospective study showed that while radiotherapy with adjuvant PCV improved progression-free survival compared to concurrent and adjuvant TMZ, it did not improve overall survival and was associated with a higher frequency of grade 3 or greater toxicity [9]. The results of the interim analysis of the CANTON trial, which evaluated TMZ-based treatment in patients with grade 3 IDH-mutant/1p19q non-codeleted astrocytoma showed that compared to adjuvant radiotherapy alone, radiotherapy with adjuvant TMZ significantly improved overall survival with a hazard ratio of 0.48 [10]. Despite the interim nature of the results, the panel considered radiotherapy with adjuvant TMZ with or without concurrent TMZ to be the preferred option for patients with grade 3 IDH-mutant/1p19q non-deleted astrocytoma during the crisis period, given the lower toxicity profile compared to the PCV regimen and the promising results from the CANTON trial. However, the panel was unable to conclude whether the addition of concurrent TMZ to adjuvant TMZ further improves outcomes for this cohort. As such, the panel made a weak recommendation for radiotherapy with concurrent and adjuvant TMZ for this cohort during the crisis period. During the non-crisis period, the NCCN guideline indicates a uniform consensus favoring either radiotherapy with concurrent and adjuvant TMZ or radiotherapy with adjuvant TMZ, based upon lower-level evidence [3]. For patients with KPS <60, the panel highly recommended best supportive care alone as the preferred option,

followed by adjuvant radiotherapy alone, given the rarity of randomized studies in this cohort and the crisis situation.

Newly diagnosed glioblastoma

In the current survey for the optimal adjuvant treatment and radiotherapy dose-fractionation schedule in newly diagnosed glioblastoma during crisis period, radiotherapy plus TMZ and radiotherapy of 40 Gy in 15 fractions were the most preferred treatment in most scenarios. Of note, despite the shortage of radiotherapy resources, conventionally fractionated standard radiotherapy of 60 Gy in 30 fractions was the most preferred regimen in 64-year-old patients with good performance status regardless of extent of resection and methylation status of the *MGMT* promoter. Additionally, despite the presence of published NOA-08 and Nordic trials where TMZ alone was proven to be potentially equivalent to radiotherapy alone (60 Gy in 30 fractions) [11,12], TMZ alone was not the preferred adjuvant treatment even in patients aged over 70 years with KPS 60 and methylated *MGMT* promoter.

The most preferred hypofractionated radiotherapy regimen during crisis was 40 Gy in 15 fractions which reflects the seldom usage of 34 Gy in 10 fractions and 25 Gy in 5 fractions in Korea, similar to the limited worldwide experience in Europe and USA [13]. Compared to the results of the KROG 21-05 survey study in elderly patients with newly diagnosed glioblastoma where 60 Gy in 30 fractions was the most preferred regimen except for 75-year-old patients with KPS of 60 [14], in the current survey assuming a crisis setting with shortage of radiotherapy resources, the utilization of conventionally fractionated standard radiotherapy was lower. Although the international expert guideline published by Bernhardt et al. [13] recommends hypofractionated radiotherapy in 3 weeks even for favorable patients (young age and good performance status) with glioblastoma during the crisis phase of COVID-19, our expert panels preferred conventionally fractionated radiotherapy in 6 weeks for these favorable patients. In contrast, in patients aged over 70 years or with poor performance status, it seems that a higher portion of physicians prefer an abbreviated course of radiotherapy during the crisis period compared to usual practice which was observed in the KROG 21-05 study [12]. This is probably because only a few retrospective studies support the use of conventionally fractionated standard radiotherapy in elderly patients with newly diagnosed glioblastoma [15]. However, since the respondents were not identical, these results should be interpreted with caution.

Newly diagnosed symptomatic brain metastases

In the current survey on symptomatic brain metastases during crisis, radiosurgery was the most preferred treatment in patients with limited number of metastases recommended by the EANO–ESMO Clinical Practice Guidelines and the ASCO-SNO-ASTRO Guideline [16,17]. Of note, despite the shortage of medical resources, 30 Gy in 10 fractions was preferred over 20 Gy in 5 fractions for whole brain radiotherapy in patients with 10 brain metastases and KPS of 70. Although 1-week whole brain radiotherapy is widely used in the clinic [16,18], physicians seem to prefer a potentially better intracranial disease control with higher doses even in the crisis setting [19].

Newly diagnosed atypical meningioma

During the COVID-19 pandemic, some groups have suggested that even elective surgery for meningiomas can be postponed in case of shortage in medical resources [20]. In our survey, most respondents chose surveillance as the preferred adjuvant strategy during the crisis period in patients with newly diagnosed atypical meningioma for cases where the tumor is completely resected and the mitotic count is low (Table 5), which is a considerable option according to international practice guidelines [21,22]. Furthermore, for 82-year-old elderly patients, most respondents also recommended surveillance after gross total resection. This is probably due to the relatively high local control around 70% at 5 years [23], and the consideration of the shortage of medical resources. In contrast, despite the shortage of radiotherapy resources, most respondents chose to proceed with adjuvant radiotherapy in patients with completely resected tumor but high mitotic counts.

Although 54 Gy in 30 fractions was the most preferred radiotherapy dose-fractionation schedule, a similar portion of respondents also chose 60 Gy in 30 fractions (results not shown). Both regimens are recommended by published guidelines [21,22]. However, despite the shortage of radiotherapy resources during the crisis period, only 1 respondent chose hypofractionated radiotherapy in 2 case-scenarios. Since short-course hypofractionated radiotherapy and radiotherapy doses under 50 Gy result in poor disease control in grade 2 or 3 meningiomas [24,25], and most neuro-oncologists have limited experience in utilizing short-course hypofractionated radiotherapy in atypical meningiomas, our expert panel concluded 54–60 Gy as the optimal radiotherapy dose even in the crisis period as for non-crisis clinical settings.

Conclusions

The results of this survey could be a useful resource for the treatment of brain tumor patients in crisis situations that could cause shortages of medical resources, such as COVID-19, which may occur again in the future. Even in the midst of crisis situations, it remains imperative to endeavor towards providing optimal treatment modalities that may enhance patient survival rates and maximize their quality of life.

Supplementary Materials

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Availability of Data and Material

All data generated or analyzed during the study are included in this published article and its supplementary information files.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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None

REFERENCES

- van den Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet 2005;366:985-90.
- Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, et al. Radiation plus procarbazine, CCNU, and vincristine in lowgrade glioma. N Engl J Med 2016;374:1344-55.
- Horbinski C, Nabors LB, Portnow J, Baehring J, Bhatia A, Bloch O, et al. NCCN Guidelines[®] insights: central nervous system cancers, version 2.2022. J Natl Compr Canc Netw 2023;21:12-20.
- Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol 2013;31:337-43.
- Cairncross JG, Wang M, Jenkins RB, Shaw EG, Giannini C, Brachman DG, et al. Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH. J Clin Oncol 2014;32:783-90.
- Stupp R, Brada M, van den Bent MJ, Tonn JC, Pentheroudakis G; ESMO Guidelines Working Group. High-grade glioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii93-101.
- van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 2013;31:344-50.
- Jaeckle KA, Ballman KV, van den Bent M, Giannini C, Galanis E, Brown PD, et al. CODEL: phase III study of RT, RT + TMZ, or TMZ for newly diagnosed 1p/19q codeleted oligodendroglioma. Analysis from the initial study design. Neuro Oncol 2021;23:457-67.

- Esteyrie V, Dehais C, Martin E, Carpentier C, Uro-Coste E, Figarella-Branger D, et al. Radiotherapy plus procarbazine, lomustine, and vincristine versus radiotherapy plus temozolomide for IDH-mutant anaplastic astrocytoma: a retrospective multicenter analysis of the French POLA cohort. Oncologist 2021;26:e838-46.
- van den Bent MJ, Tesileanu CMS, Wick W, Sanson M, Brandes AA, Clement PM, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol 2021;22:813-23.
- Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 2012;13:707-15.
- Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, et al. 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 2012;13:916-26.
- Bernhardt D, Wick W, Weiss SE, Sahgal A, Lo SS, Suh JH, et al. Neurooncology management during the COVID-19 pandemic with a focus on WHO grade III and IV gliomas. Neuro Oncol 2020;22:928-35.
- Wee CW, Yoon HI, Lee SW, Lim DH. Current trend of radiotherapy for glioblastoma in the elderly: a survey study by the brain tumor Committee of the Korean Radiation Oncology Group (KROG 21-05). Jpn J Clin Oncol 2022;52:843-9.
- Wee CW, Kim IH, Park CK, Kim N, Suh CO, Chang JH, et al. Chemoradiation in elderly patients with glioblastoma from the multi-institutional GBM-molRPA cohort: is short-course radiotherapy enough or is it a matter of selection? J Neurooncol 2020;148:57-65.
- Le Rhun E, Guckenberger M, Smits M, Dummer R, Bachelot T, Sahm F, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol 2021;32:1332-47.
- Vogelbaum MA, Brown PD, Messersmith H, Brastianos PK, Burri S, Cahill D, et al. Treatment for brain metastases: ASCO-SNO-ASTRO guideline. J Clin Oncol 2022;40:492-516.
- Rades D, Bohlen G, Dunst J, Lohynska R, Veninga T, Stalpers L, et al. Comparison of short-course versus long-course whole-brain radiotherapy in the treatment of brain metastases. Strahlenther Onkol 2008;184: 30-5.
- Graham PH, Bucci J, Browne L. Randomized comparison of whole brain radiotherapy, 20 Gy in four daily fractions versus 40 Gy in 20 twice-daily fractions, for brain metastases. Int J Radiat Oncol Biol Phys 2010;77:648-54.
- Neuro-oncology treatment guidance during COVID-19 pandemic. London: Royal College of Radiologists [updated March 27, 2020]. (Accessed March 3, 2023, at https://www.rcr.ac.uk/sites/default/files/neuro-oncology-treatment-covid-19.pdf.)
- 21. Goldbrunner R, Stavrinou P, Jenkinson MD, Sahm F, Mawrin C, Weber DC, et al. EANO guideline on the diagnosis and management of meningiomas. Neuro Oncol 2021;23:1821-34.
- NCCN clinical practice guidelines in oncology. Central nervous system cancers. Plymouth Meeting, PA: NCCN [updated 2022]. (Accessed March 3, 2023, at https://www.nccn.org/professionals/physician_gls/ pdf/cns.pdf.)
- Byun HK, Chang WI, Lee JH, Park CK, Kim IA, Kim CY, et al. Adjuvant radiotherapy versus surveillance for grade 2 intracranial meningiomas: a multi-institutional propensity score-matched study. Front Oncol 2022;12:877244.
- Dziuk TW, Woo S, Butler EB, Thornby J, Grossman R, Dennis WS, et al. Malignant meningioma: an indication for initial aggressive surgery and adjuvant radiotherapy. J Neurooncol 1998;37:177-88.
- 25. Sarhan N, Abduljabbar L, Laperriere N, Shultz D, Asha M, Zadeh G, et al. Short course hypofractionated radiotherapy for frail or elderly patients with meningioma. Cureus 2020;12:e8604.