ORIGINAL ARTICLE Brain Tumor Res Treat 2020;8(1):20-28 / pISSN 2288-2405 / eISSN 2288-2413
https://doi.org/10.14791/btrt.2020.8.e7

Check for updates

A National Consensus Survey for Current Practice in Brain Tumor Management III: Brain Metastasis and Primary Central Nervous System Lymphoma

Sung Kwon Kim[1*], Ji Eun Park[2*], Kyung Hwan Kim[3*], Jin Mo Cho[4*], Jangsup Moon[5], Wan-Soo Yoon[6], Se Hoon Kim[7], Young Il Kim[8], Young Zoon Kim[9], Ho Sung Kim[2], Yun-Sik Dho[10], Jae-Sung Park[11], Hong In Yoon[12], Youngbeom Seo[13], Kyoung Su Sung[14], Jin Ho Song[15], Chan Woo Wee[16], Se-Hoon Lee[17], Do Hoon Lim[18], Jung Ho Im[19], Jong Hee Chang[20], Myung-Hoon Han[21], Je Beom Hong[22], Kihwan Hwang[23], Chul-Kee Park[24†], Youn Soo Lee[25†], Ho-Shin Gwak[26†], KSNO Guideline Working Group

Received February 29, 2020
Revised March 2, 2020
Accepted March 16, 2020

Correspondence
Chul-Kee Park
Department of Neurosurgery,
Seoul National University Hospital,
Seoul National University
College of Medicine,
101 Daehak-ro, Jongno-gu,
Seoul 03080, Korea
Tel: +82-2-2072-0347
Fax: +82-504-154-4633
E-mail: nsckpark@snu.ac.kr

Youn Soo Lee
Department of Hospital Pathology,
Seoul St. Mary's Hospital,
College of Medicine,
The Catholic University of Korea,
222 Banpo-daero, Seocho-gu,
Seoul 06591, Korea
Tel: +82-2-2258-1626
Fax: +82-2-2258-1628
E-mail: lys9908@catholic.ac.kr

Ho-Shin Gwak
Department of Cancer Control,
Graduate School of Cancer Science and Policy, National Cancer Center,
323 Ilsan-ro, Ilsandong-gu,
Goyang 10408, Korea
Tel: +82-31-920-1666
Fax: +82-31-920-2798
E-mail: nsghs@ncc.re.kr

*These authors contributed equally to this work as a first author.
†These authors contributed equally to this work as a corresponding author.

Background The Guideline Working Group of the Korean Society for Neuro-Oncology (KSNO) conducted the nationwide questionnaire survey for diverse queries facing to treat patients with brain tumor. As part III of the survey, the aim of this study is to evaluate the national patterns of clinical practice for patients with brain metastasis and primary central nervous system lymphoma (PCNSL).

Methods A web-based survey was sent to all members of the KSNO by email. The survey included 7 questions of brain metastasis and 5 questions of PCNSL, focused on the management strategies in specific situations. All questions were developed by consensus of the Guideline Working Group.

Results In the survey about brain metastasis, respondents preferred surgical resection with adjuvant treatment for patients with a surgically accessible single brain metastatic lesion less than 3 cm in size without extracranial systemic lesions. However, most respondents considered radiosurgery for surgically inaccessible lesions. As the preferred treatment of multiple brain metastases according to the number of brain lesions, respondents tended to choose radiotherapy with increasing number of lesions. Radiosurgery was mostly chosen for the brain metastases of less than or equal to 4. In the survey about PCNSL, a half of respondents choose high-dose methotrexate-based polychemotherapy as the first-line induction therapy for PCNSL. The consolidation and salvage therapy showed a little variation among respondents. For PCNSL patients with cerebrospinal fluid dissemination, intrathecal chemotherapy was most preferred.

Conclusion The survey demonstrates the prevailing clinical practice patterns for patients with brain metastasis and PCNSL among members of the KSNO. This information provides a point of reference for establishing a practical guideline in the management of brain metastasis and PCNSL.

Key Words Korean Society for Neuro-Oncology; Practice patterns; Brain tumors; Metastasis; Lymphoma, Guideline Working Group.

INTRODUCTION

The Guideline Working Group of Korean Society for Neuro-Oncology (KSNO) conducted a nationwide questionnaire survey on the clinical practice about several topics of brain tumor. The intent of this survey study is described in the previous article of the series in this issue. As part III of the survey, this study deals with practical decisions in the management of brain metastasis and primary central nervous system lymphoma (PCNSL).

Brain metastases are the most common CNS tumors, with up to 30−40% of cancer patients developing brain metastases [1]. The management of brain metastases varies according to accessibility for surgical management, number of lesions, patients' clinical status, and physicians' preferences. According to National Comprehensive Cancer Network (NCCN) guidelines, surgery is recommended for a limited number of metastases with lower level evidence (category 2A) [2], but no solid management guideline exists for extensive metastases or recurrent disease. A paucity of evidence and different clinical situations formed varied practice patterns across centers [3], and key questions for management strategies for brain metastases include following: single metastasis with or without surgical accessibility, disease status with or without systemic involvement, and local or multiple recurrence after initial therapy.

PCNSL is a rare brain tumor and represents 3−4% of all brain tumors [4]. PCNSL is a highly aggressive non-Hodgkin lymphoma that is typically restricted to the brain, spine, cerebrospinal fluid (CSF), and eyes without evidence of systemic spread [5]. High-dose methotrexate (HD-MTX) plus consolidation chemotherapy and/or whole brain radiotherapy (WBRT) is the mainstay of standard of care for newly diagnosed PCNSL [6]. However, the optimal treatment regimen has yet to be defined. In addition, no consensus exists for refractory and relapsed PCNSL. Questions in this study deal with current controversies including the optimal chemotherapy regimen, the role of radiation, the salvage management, and treatment of the CSF space [5].

The aim of this study is to evaluate the current status of clinical practice for patients with brain metastasis and PCNSL from the nationwide survey in Korea.

MATERIALS AND METHODS

The details of the study design, outline, and implementation are described in the previous article of the series in this issue. Here, the questionnaires about brain metastases (7 questions) and PCNSL (5 questions) were structured around existing controversies regarding real clinical management in patients (Appendix).

Regarding to the brain metastasis, the survey questions dealt with the following specific situations related with the management plan of brain metastasis patient: 1) Single brain metastasis (initial management) depending on size; 2) Multiple brain metastases (initial management) depending on symptom, location, and number of lesions; 3) Progressive single brain metastasis with a failure of initial management; and 4) Progressive multiple brain metastases.

As for the PCNSL, the questionnaires were structured general questions focused on the diagnostic work-ups and treatment options. All responses were analyzed descriptively as well as quantitatively wherever appropriate.

RESULTS

Brain metastasis

The results of a survey on single brain metastasis management options are shown in Fig. 1. For patients with a surgically accessible single brain metastatic lesion with size less than 3 cm in diameter, 32 of 49 (65.3%) respondents preferred the surgical resection without (n=4) or with postoperative managements such as, chemotherapy (n=2), WBRT (n=5), and radiation boost to the surgical cavity (n=21). Seventeen (34.7%) respondents have chosen radiosurgery (n=16) and localized radiotherapy (n=1) without surgery as an initial treatment for the same lesion. However, if the patient has a surgically inaccessible single brain metastatic lesion less than 3 cm in diameter without any other evidence of systemic disease, most respondents (n=44, 89.8%) preferred the radiosurgery (including fractionated method) than localized radiotherapy (n=4, 8.2%) or WBRT (n=1, 2.0%).

For those patients with multiple brain metastases but if one of the lesions is showing mass effect and surgically accessible, most respondents (n=42, 85.7%) choose the surgical resection of the mass of interest followed by adjuvant treatment for the other lesions with radiosurgery in 8.2% (n=4), or radiotherapy in 6.1% (n=3). There was similar tendency for choosing treatment modalities according to the number of lesions between conditions having extracranial metastases or not (Fig. 2). Respondents considered the radiotherapy as the number of brain lesions increased, and the radiosurgery was mainly chosen at the brain metastases of less than or equal to 4. The consideration of chemotherapy combination increased when there were extracranial systemic lesions.

For enlarging single brain metastasis, which had been treated with radiosurgery or radiotherapy 3 months ago, respondents considered the following options: short-term follow-up MRI within 1 or 2 months (n=31, 63.3%); decision-making after further work-up such as positron emission tomography

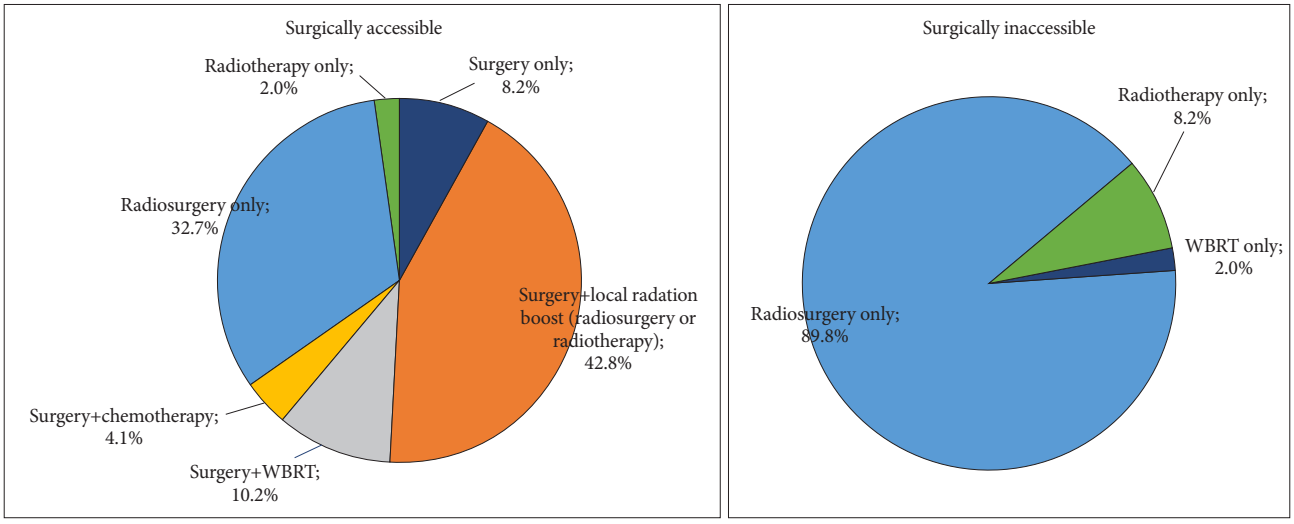

Fig. 1. Preferred management options in patients with small (diameter less than 3 cm) single brain metastasis without any evidence of systemic disease. WBRT, whole brain radiotherapy.

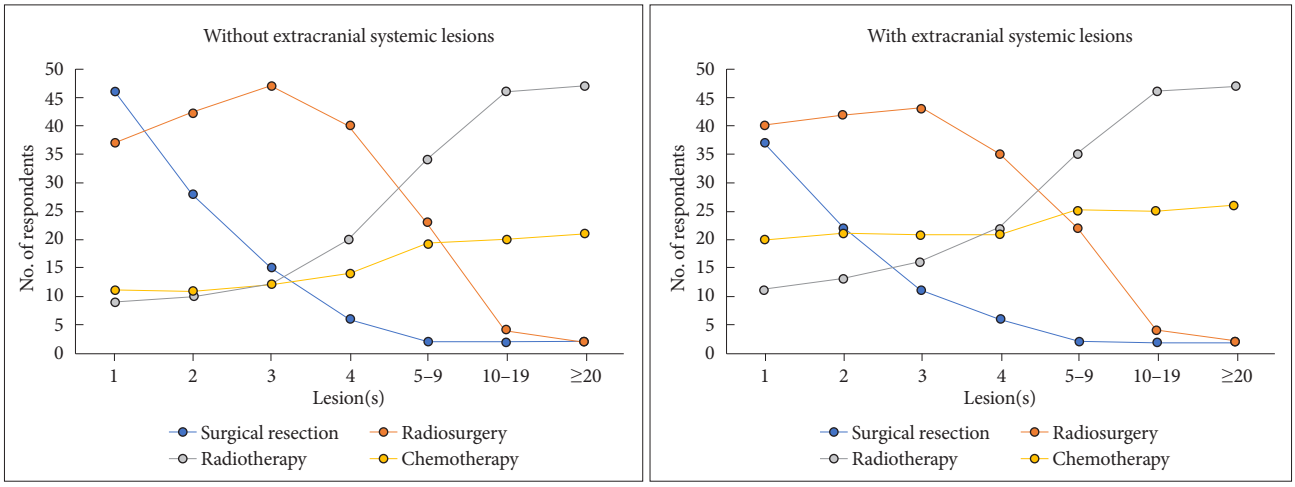

Fig. 2. Treatment modality preference according to the number for multiple brain metastases brain lesions without extracranial systemic lesions or with extracranial systemic lesions.

(PET) and MR perfusion (n=7, 14.3%); surgical resection followed by adjuvant treatment such as radiotherapy, radiosurgery, and chemotherapy (n=4, 8.2%); surgical resection only (n=4, 8.2%). Fig. 3 shows preference of respondents for the treatment strategies for patients with developing multiple brain metastases after treatment of single brain metastasis according to previously treated modality. Localized radiotherapy or WBRT was the mainstay of the multiple metastases (n=36–38, 78.3–84.4%), regardless the patients were treated with surgery, radiosurgery, or chemotherapy. When the patients had a history of radiotherapy, radiosurgery (n=22, 48.9%) was considered. Chemotherapy was preferred as combined therapy for radiosurgery, radiotherapy, and surgery.

PCNSL

Respondents were answered to consider following diagnostic work-ups to identify the extent of PCNSL; brain MRI scan (including enhance, diffusion and perfusion images) (n=46, 100%), ophthalmologic evaluation (n=38, 82.6%), whole-body PET scan (n=36, 78.3%), chest and/or abdominopelvic CT scan (n=32, 69.6%), spine MRI scan (if symptomatic) (n=31, 67.4%), CSF analysis (n=31, 67.4%), brain CT scan (n=25, 54.3%), bone marrow biopsy (n=17, 37.0%), testicular ultrasound for men >60 years (n=11, 23.9%), and serum LDH (n=1, 2.2%).

It was surprising to see that there is still a weak consensus on the initial management protocol for PCNSL. As a first-line induction therapy for PCNSL, 22 of 44 (50.0%) respondents considered HD-MTX-based polychemotherapy with (n=5) or without rituximab (n=17). Sixteen (36.4%) respondents used single-agent HD-MTX and six (13.6%) choose WBRT with or without chemotherapy. As the consolidation therapy for those

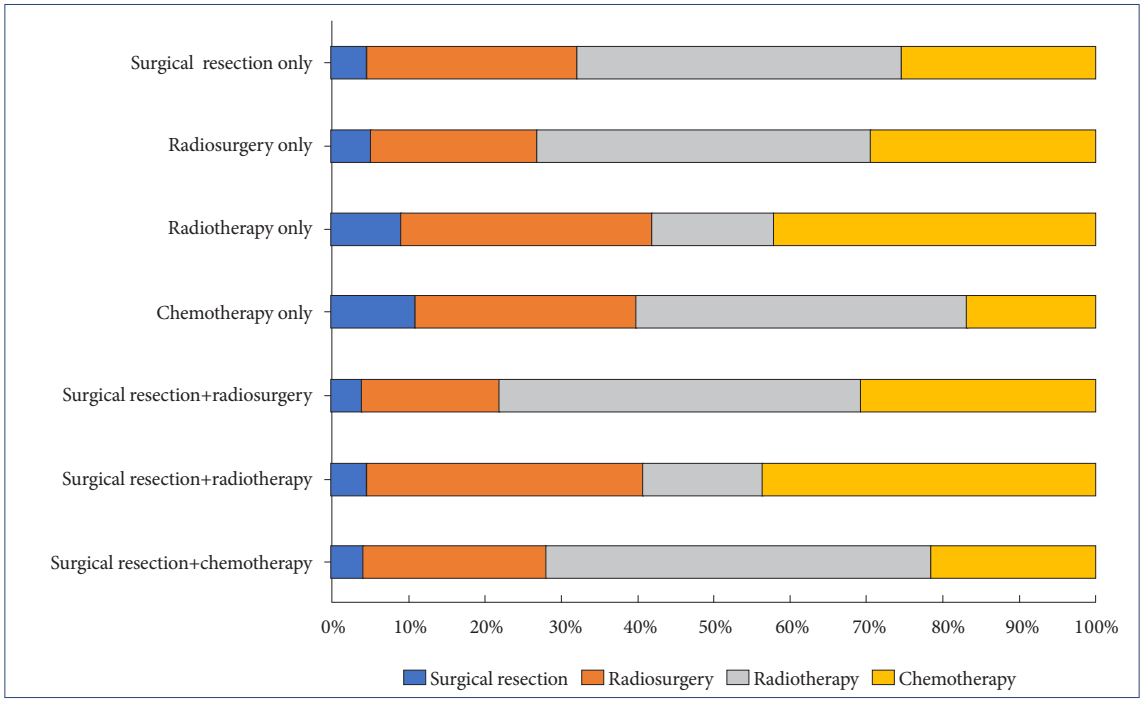

Fig. 3. Treatment modality preference according to the previous treatment method for patients with developing multiple brain metastasis after treatment of single brain metastasis. Color affiliations are the previous initial treatment modalities undertaken.

patients showing complete response after induction therapy, 18 of 40 (42.5%) respondents choose high-dose WBRT at 45 Gy (n=3) or low-dose WBRT at 23−24 Gy (n=15). One respondent stated that the low-dose WBRT was given only to young patients. However, 19 of 40 (47.5%) respondents considered chemotherapy as the consolidation therapy. The regimens were as followings: continuing HD-MTX based chemotherapy (n=12); high-dose chemotherapy with autologous stem cell transplantation (ASCT) (n=6); conventional chemotherapy using cytarabine, etoposide plus cytarabine, or others (n=1). Three respondents (7.5%) choose the close observation without consolidation therapy.

As the salvage therapy for patients showing partial response (PR), progressive disease (PD), and recurrence after induction therapy, 14 of 42 (33.3%) respondents choose the WBRT with (n=3) or without local boost (n=11). Sixteen (38.1%) respondents choose the HD-MTX based chemotherapy and WBRT rechallenge and four (9.5%) respondents choose the single or combined chemotherapy using temozolomide, pemetrexed, topotecan, or rituximab. Four (9.5%) respondents considered ASCT and three (7.1%) considered the clinical trial. In free text response, one respondent stated that chemotherapy was performed for patients with PR or PD, and WBRT was performed for recurred patients. Fig. 4 shows the preferred management of respondents for PCNSL patients with CSF dissemination.

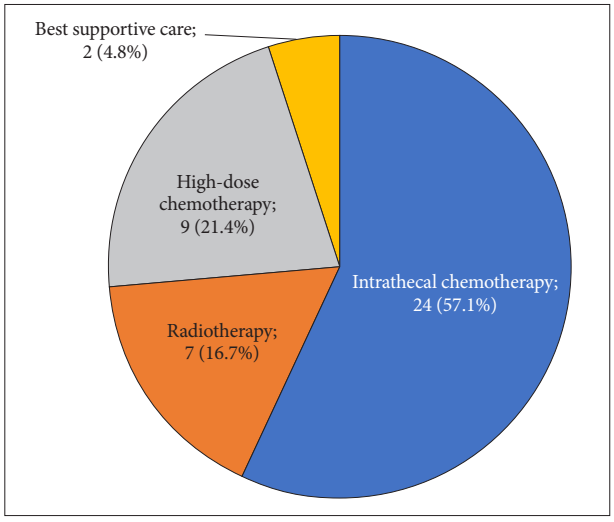

Fig. 4. Pie chart showing the management preference of respondents for primary central nervous system lymphoma with cerebrospinal fluid dissemination.

DISCUSSION

The majority of practice patterns for single brain metastasis in Korea was consistent with the NCCN guideline. The mainstay of management for accessible single metastasis was surgery (65.3%) with or without adjuvant radiation at the surgical cavity, followed by radiosurgery (32.7%). This is in line with current evidence that the local control rate of brain metastases

was comparable between radiosurgery and surgical resection group [7]. The preference options for the management for single brain metastasis was similar to those from international survey by radiation oncologists [3] who had chosen surgery and WBRT (40%), radiosurgery and WBRT (17%), and radiosurgery alone (14%).

Interestingly, surgery was preferred (85.7%) for the symptomatic lesion among the multiple metastases when it is surgically accessible. This result is different from an international survey by radiation oncologists that 53% would not offer surgery but give WBRT for multiple brain metastases [3]. The reason for that is the main respondents of our survey was neurosurgeons (66.7%), followed by radiation oncologists (24.1%).

Imaging findings after radiotherapy and radiosurgery can be confounded by treatment effects [8]. Physicians preferred to repeat scan with short-term interval of 1−2 month rather than additional advanced MRI or PET for enlarging single metastasis after radiosurgery or radiotherapy. When diagnosed with multiple recurrences, localized radiotherapy or WBRT was the most preferred treatment option, combination with chemotherapy.

PCNSL is usually present as a single brain lesion, but sometimes involves eyes, CSF, and rarely the spinal cord [9]. Thorough clinical evaluation of PCNSL is mandatory to assess the extent of the disease and to treat patients. Practical guidelines from the NCCN and European Association for Neuro-Oncology (EANO) commonly recommend ophthalmologic exam, CSF exam, spine MRI (if symptomatic), chest/abdominopelvic CT or whole-body PET/CT scan, bone marrow biopsy (lower level evidence), and testicular sonography (lower level evidence) [10]. The result of the survey in terms of clinical evaluation is generally in accordance with NCCN and EANO guidelines while both bone marrow biopsy and testicular sonography are performed less frequently.

In this survey, HD-MTX based chemotherapy with or without other chemotherapeutic agents is revealed as a main strategy for the induction therapy. In prospective studies, HD-MTX chemotherapy yielded a 52−100% response rate, while HD-MTX-based polychemotherapy resulted in 65−100% response rate [6,11-13]. NCCN and EANO guidelines recommend that chemotherapy should include HD-MTX at doses of at least 3g/m^2 [10]. Interestingly, a minority of respondents use polychemotherapy including rituximab, a monoclonal antibody directed against CD20 of the B-cell for CD20 positive PCNSL. The result of the IELSG32 phase 2 trial suggests that the combination of HD-MTX, cytarabine, thiotepa, and rituximab (MATRix regimen) as the first-line treatment improves overall response rates [14]. To date, the level of evidence supporting the use of rituximab as part of protocol remains low, but several trials are ongoing to verify that addition of rituximab to induction therapy is beneficial [10].

Nearly half of clinicians choose the WBRT, especially low-dose WBRT, as a main strategy for consolidation in this survey. In the largest and only phase 3 trial (G-PCNSL-SG 1) comparing consolidation WBRT to observation alone, the overall survival was similar in patients underwent WBRT and those who did not [15]. In addition, high-dose WBRT negatively impacts on quality of life without the survival benefit in patients with PCNSL [16]. In accordance with the survey result, practical guidelines recommend reduced-dose consolidation radiotherapy. Consolidation therapies based on continued HD-MTX chemotherapy, high-dose chemotherapy combined with ASCT, or other chemotherapeutic regimens are also revealed as preferred treatment options in practice.

Despite advances in first-line treatment, half of respondent relapse and a third of PCNSL patients have primary refractory disease [6]. The salvage regimen is poorly defined and varied widely including HD-MTX rechallenge, temozolomide, topotecan, WBRT, rituximab, ASCT, and so on [17]. As the survey result for the salvage treatment, HD-MTX rechallenge or WBRT for those who have not received previously seems to be effective in retrospective studies [18,19]. For the CSF disseminated disease, more than half of respondents choose intrathecal chemotherapy although no consensus exists regarding the role of intrathecal chemotherapy until now. Overall decision of salvage treatments should have been made based on patients' situation and clinicians' experiences.

As with any online survey, the major limitation of this study is response bias that respondents might be influenced by the pressure to follow the published guidelines, especially in the survey of PCNSL because of relatively few medical oncologists of the KSNO members. Additionally, the relatively low response rate may give rise to sampling bias interfering with the valuable interpretation of several questions.

In conclusion, the survey demonstrates the variation and similarity of clinical practice for patients with brain metastasis and PCNSL among members of the KSNO. We could draw important issues to be studied for the establishment of guidelines based on the best available evidence.

Conflicts of Interest

The authors have no potential conflicts of interest.

Acknowledgments

None

ORCID iDs

Chul-Kee Park https://orcid.org/0000-0002-2350-9876
Youn Soo Lee https://orcid.org/0000-0002-1653-6315
Ho-Shin Gwak https://orcid.org/0000-0001-7175-4553
Sung Kwon Kim https://orcid.org/0000-0002-7074-9290
Ji Eun Park https://orcid.org/0000-0002-4419-4682

Kyung Hwan Kim https://orcid.org/0000-0003-1244-6969
Jin Mo Cho https://orcid.org/0000-0002-1192-8993

Author Affiliations

[1]Department of Neurosurgery, Gyeongsang National University Changwon Hospital, Gyeongsang National University School of Medicine, Changwon, Korea; [2]Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [3]Department of Neurosurgery, Chungnam National University Hospital, Chungnam National University School of Medicine, Daejeon, Korea; [4]Department of Neurosurgery, International St. Mary's Hospital, Catholic Kwandong University, Incheon, Korea; [5]Department of Neurology, Rare Disease Center, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea; [6]Department of Neurosurgery, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea; [7]Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [8]Department of Neurosurgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea; [9]Division of Neurooncology and Department of Neurosurgery, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea; [10]Department of Neurosurgery, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea; [11]Department of Neurosurgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea; [12]Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea; [13]Department of Neurosurgery, Yeungnam University Hospital, Yeungnam University College of Medicine, Daegu, Korea; [14]Department of Neurosurgery, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Korea; [15]Department of Radiation Oncology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea; [16]Department of Radiation Oncology, SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea; [17]Division of Hematology/Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [18]Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [19]Department of Radiation Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea; [20]Department of Neurosurgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [21]Department of Neurosurgery, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Korea; [22]Department of Neurosurgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea; [23]Department of Neurosurgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea; [24]Department of Neurosurgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea; [25]Department of Hospital Pathology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea; [26]Department of Cancer Control, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Korea

REFERENCES

1. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. J Neurooncol 2005;75:5-14.
2. Nabors LB, Portnow J, Ammirati M, et al. NCCN Guidelines Insights: central nervous system cancers, version 1.2017. J Natl Compr Canc Netw 2017;15:1331-45.
3. Tsao MN, Rades D, Wirth A, et al. International practice survey on the management of brain metastases: Third International Consensus Workshop on Palliative Radiotherapy and Symptom Control. Clin Oncol (R Coll Radiol) 2012;24:e81-92.
4. Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer 2011;105:1414-8.
5. Grommes C, DeAngelis LM. Primary CNS lymphoma. J Clin Oncol 2017;35:2410-8.
6. Kerbauy MN, Moraes FY, Lok BH, et al. Challenges and opportunities in primary CNS lymphoma: a systematic review. Radiother Oncol 2017; 122:352-61.
7. Churilla TM, Chowdhury IH, Handorf E, et al. Comparison of local control of brain metastases with stereotactic radiosurgery vs surgical resection: a secondary analysis of a randomized clinical trial. JAMA Oncol 2019;5:243-7.
8. Pope WB. Brain metastases: neuroimaging. Handb Clin Neurol 2018; 149:89-112.
9. Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol 2003;21:266-72.
10. Hoang-Xuan K, Bessell E, Bromberg J, et al. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology. Lancet Oncol 2015; 16:e322-32.
11. Batchelor T, Carson K, O'Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. J Clin Oncol 2003;21:1044-9.
12. Guha-Thakurta N, Damek D, Pollack C, Hochberg FH. Intravenous methotrexate as initial treatment for primary central nervous system lymphoma: response to therapy and quality of life of patients. J Neurooncol 1999;43:259-68.
13. Herrlinger U, Schabet M, Brugger W, et al. German Cancer Society Neuro-Oncology Working Group NOA-03 multicenter trial of single-agent high-dose methotrexate for primary central nervous system lymphoma. Ann Neurol 2002;51:247-52.
14. Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol 2016;3:e217-27.
15. Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol 2010; 11:1036-47.
16. Herrlinger U, Schäfer N, Fimmers R, et al. Early whole brain radiotherapy in primary CNS lymphoma: negative impact on quality of life in the randomized G-PCNSL-SG1 trial. J Cancer Res Clin Oncol 2017;143: 1815-21.
17. Langner-Lemercier S, Houillier C, Soussain C, et al. Primary CNS lymphoma at first relapse/progression: characteristics, management, and outcome of 256 patients from the French LOC network. Neuro Oncol 2016;18:1297-303.
18. Nguyen PL, Chakravarti A, Finkelstein DM, Hochberg FH, Batchelor TT, Loeffler JS. Results of whole-brain radiation as salvage of methotrexate failure for immunocompetent patients with primary CNS lymphoma. J Clin Oncol 2005;23:1507-13.
19. Plotkin SR, Betensky RA, Hochberg FH, et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. Clin Cancer Res 2004;10:5643-6.

Appendix

Brain metastasis

1. For patients with a surgically accessible single brain metastasis less than 3 cm in size without extracranial systemic lesions, what treatment would you recommend for patients?
   ( ) Surgical resection alone
   ( ) Surgical resection with postoperative radiation boost to the surgical cavity
   ( ) Surgical resection with postoperative whole brain radiotherapy
   ( ) Surgical resection with postoperative chemotherapy
   ( ) Radiosurgery alone
   ( ) Localized Radiotherapy alone
   ( ) Whole brain radiotherapy alone
   ( ) Chemotherapy alone
2. For patients with a surgically inaccessible (e.g. brainstem) single brain metastasis less than 3 cm in size without extracranial systemic lesions, what treatment would you recommend for patients?
   ( ) Radiosurgery alone
   ( ) Localized radiotherapy alone
   ( ) Whole brain radiotherapy alone
   ( ) Chemotherapy alone
3. For patients with one symptomatic surgically accessible brain metastatic lesion with mass effect and the other asymptomatic lesions without mass effect, do you recommend the surgical resection?
   ( ) Yes, I recommend surgical resection with postoperative further treatment.
   ( ) No, I recommend radiosurgery.
   ( ) No, I recommend radiotherapy.
   ( ) No, I recommend chemotherapy.
4. For patients without extracranial systemic lesions, what treatment would you recommend for patients according to the number of brain metastatic lesions? (Choose all that apply)
   a) One lesion
      ( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
   b) Two lesions
      ( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
   c) Three lesions
      ( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
   d) Four lesions
      ( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
   e) Five to nine lesions
      ( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
   f) Ten to nineteen lesions
      ( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
   g) More than twenty lesions
      ( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
5. For patients with extracranial systemic lesions, what treatment would you recommend for patients according to the number of brain metastatic lesions? (Choose all that apply)
   a) One lesion
      ( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
   b) Two lesions
      ( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
   c) Three lesions
      ( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy

d) Four lesions
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
e) Five to nine lesions
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
f) Ten to nineteen lesions
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
g) More than twenty lesions
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy

6. For patients with enlarging single brain metastasis on 3 months follow-up MRI after treatment radiosurgery or radiotherapy, what treatment would you recommend for patients?
( ) Short-term follow-up MRI check within 1 or 2 months
( ) Decision-making after further work-up such as PET and MR perfusion
( ) Repeat surgical resection alone
( ) Repeat surgical resection followed by adjuvant treatment
( ) Repeat radiosurgery or radiotherapy alone
( ) Other
7. For patients with developing multiple brain metastases on 3 months follow-up MRI after treatment of single brain metastasis, what treatment would you recommend for patients according to previously treated modality? (Choose all that apply)
a) Surgical resection only
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
b) Radiosurgery only
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
c) Radiotherapy only
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
d) Chemotherapy only
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
e) Surgical resection and radiosurgery
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
f) Surgical resection and radiotherapy
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy
g) Surgical resection and chemotherapy
( ) Surgical resection ( ) Radiosurgery ( ) Radiotherapy ( ) Chemotherapy

PCNSL

1. What work-ups do you perform to identify the extent of PCNSL in your institution? (Choose all that apply)
( ) Brain CT scan
( ) Brain MRI scan (including enhance, diffusion and perfusion images)
( ) Spine MRI scan (if symptom exist)
( ) Ophthalmologic evaluation
( ) CSF analysis
( ) Whole-body PET scan
( ) Chest and/or abdominopelvic CT scan
( ) Bone marrow biopsy
( ) Testicular ultrasound for men >60 years
( ) Serum LDH
( ) Other
2. What treatment do you recommend for first-line induction therapy of PCNSL in your institution?
( ) Whole-brain radiotherapy (WBRT) with or without chemotherapy
( ) Single-agent high dose methotrexate (HD-MTX)
( ) HD-MTX based polychemotherapy with cytarabine, ifosfamide or others

( ) Rituximab and HD-MTX based polychemotherapy (R-MVP, R-MT, MATRix, R-MVBP, or others)
( ) Other

3. What treatment do you recommend for consolidation therapy of PCNSL showing complete response after induction therapy in your institution?
( ) High-dose chemotherapy with autologous stem cell transplantation
( ) Conventional chemotherapy using cytarabine, etoposide plus cytarabine, or others
( ) Continue HD-MTX based chemotherapy
( ) High-dose WBRT (approximately 45 Gy)
( ) Low-dose WBRT (approximately 23−24 Gy)
( ) Observation
( ) Other

4. What treatment do you recommend for salvage therapy of PCNSL showing partial response, progressive disease and recurrence after induction therapy in your institution?
( ) HD-MTX based chemotherapy and WBRT rechallenge
( ) Single or combined chemotherapeutic agents (e.g. temozolomide, pemetrexed, topotecan, or rituximab)
( ) Autologous stem cell transplantation
( ) Consider clinical trial
( ) WBRT alone
( ) Best supportive care
( ) Other

5. What treatment do you recommend for PCNSL with CSF dissemination in your institution?
( ) Intrathecal chemotherapy
( ) Radiotherapy
( ) High-dose chemotherapy
( ) Best supportive care
( ) Other