INTRODUCTION

Leptomeningeal metastasis (LM) is a devastating and often late-stage complication of advanced solid tumors and occurring in 5–8% of patients with metastatic cancers [1-3]. LM is defined as an infiltration of the leptomeninges and cerebrospinal fluid (CSF) by malignant cells [3]. The incidence of LM is increasing due to improvement in the survival of patients with solid tumors and advances in neuroimaging modalities for detection of LM. The most common solid tumors leading to LM are breast cancer, lung cancer, and melanoma [3,4]. The clinical symptoms and signs presented in patients suggesting LM include cranial nerve palsies, headaches, cerebral disturbances, mental change, and motor weakness [3]. Standard diagnostic evaluation is the combination of CSF cytology and contrast-enhanced MRI of the brain and spine. Once LM is diagnosed, the prognosis of the disease is very poor; the median survival of patients diagnosed with LM is approximately 2–4 months [5-8].

The goals of LM treatment include improving or stabilizing the neurological symptoms, and extending survival. Radio-
therapy to the sites of symptomatic disease, systemic chemotherapy for primary tumors, and intrathecal (IT) chemotherapy are available options. Because there is no standard treatment for LM, appropriate choices and combinations of these modalities are performed according to the patient’s condition and disease state [8-10].

The aim of this retrospective study was to report the clinical characteristics and outcomes of patients with solid tumors who were diagnosed with LM, and to identify the clinical prognostic factors for survival in such patients.

MATERIALS AND METHODS

Patients
This study retrospectively analyzed the clinical data of 58 patients with solid tumors who were diagnosed LM at two university hospitals in Korea from January 2007 to December 2017.

We selected eligible subjects among patients with solid tumors who presented with symptoms or signs suggesting LM, and performed MRI of the brain (and/or spine) and CSF studies. LM was confirmed by either 1) radiologic evidences of LM on MRI of the brain and/or spine, or 2) abnormal findings of CSF analysis suggesting LM (malignant cytology; or increased proteins levels and/or increased cell counts without malignant cytology).

The patients’ clinical features, treatment information, and outcomes were retrospectively obtained from the medical records. The Institutional Review Board of two hospitals approved this study (KUGH 2018-05-043, H-1803-004-064).

Statistical analysis
Overall survival (OS) was defined as the time from the date of diagnosis of LM to the date of death from any cause. The Kaplan-Meier method was used to estimate survival, and differences between groups were analyzed by the log-rank test. Prognostic factors associated with survival were evaluated using a Cox proportional hazard model. Statistical analyses were performed using SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA), and the values of \( p < 0.05 \) were defined as statistically significant.

RESULTS

Patient characteristics
A total of 58 patients were included in this analysis. The patient characteristics are summarized in Table 1. The median age of patients at LM diagnosis was 51 years (range, 27–72 years), and 62.1% of the patients had a poor the Eastern Cooperative Oncology Group (ECOG) performance status (PS).

Diagnosis and treatment of LM
MRI studies of the brain and CSF analysis were performed for all 58 patients. Thirty patients (51.7%) underwent MRI of the spine. LM was established by both MRI and CSF analysis.
Leptomeningeal Metastasis in Solid Tumors

in 42 patients (72.4%); MRI alone in 2 (3.5%); and CSF analysis in 14 (24.1%). Of the 44 patients with positive findings of LM on MRI, 6 patients had positive findings in both the brain and spine; 28 in the brain alone (20 patients did not undergo MRI studies of the spine), and 10 in the spine alone.

Fifty-six patients (96.6%) had abnormal CSF findings suggesting LM, and 2 patients showed normal findings. Malignant cells in CSF cytology were observed in 44 patients (75.9%). All 12 patients without malignant cells but with other abnormal CSF findings showed elevated protein levels in the CSF, and 5 patients showed elevated cell counts. The protein levels and cell counts in the CSF were elevated in 42 patients (73.7%) (>50 mg/dL) (1 patient had no data on protein levels in the CSF) and 38 patients (65.5%) (>5/mm³), respectively. The glucose levels was decreased in the CSF of 26 patients (50.0%) (<50 mg/dL) (6 patients had no data on the glucose levels in CSF). Opening pressure and carcinoembryonic antigen level in the CSF were measured in 33 and 22 patients, and were elevated in 14 (42.4%) and 15 (68.2%) patients, respectively (Table 2).

Five patients (8.6%) received best supportive care only. IT chemotherapy was administered in 43 patients (74.1%), and a median 6 cycles of IT chemotherapy was performed (range, 1–35 cycles). Eight patients (13.8%) achieved negative conversions of cytology. Seventeen patients (29.3%) received radiotherapy for the brain or spine, and 24 patients (41.4%) received systemic chemotherapy after LM diagnosed. Chemotherapy containing molecular-targeted agents was performed in 6 patients (gefitinib in 4 patients with NSCLC, lapatinib and capecitabine in 1 patient with breast cancer, and trastuzumab in 1 patient with breast cancer) for LM treatment (Table 3).

Survival and prognostic factors

Among 58 patients with LM, 43 (74.1%) died by the time of analysis. The median OS of the entire cohort was 2.4 months [95% confidence interval (CI), 1.0–3.7], and the 1-year survival rate was 17.6% (Fig. 1).

Table 4 shows the results of the univariate and multivariate analyses of prognostic factors associated with survival in patients with LM. A good ECOG PS (≤2) at the time of LM diagnosis, a prior history of brain radiation, and administration of systemic chemotherapy after LM diagnosis were associated with prolonged survival in the univariate analysis (Fig. 2), and these variables showed statistical significance in the multivariate analysis.

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**Table 2.** CSF analysis findings in patients with leptomeningeal metastasis

| Parameters                     | Number of patients/total patients n/n (%) |
|--------------------------------|----------------------------------------|
| Positive malignant cytology    | 44/58 (75.9)                           |
| Pleocytosis (cells >5/mm³)     | 38/58 (65.5)                           |
| Elevated protein (protein >50 mg/dL) | 42/57 (73.7)                           |
| Increased ICP (opening pressure >20 cm H₂O) | 14/33 (42.4)                           |
| Decreased glucose (glucose <50 mg/dL) | 26/52 (50.0)                           |
| Elevated CEA (CEA >5 ng/dL)    | 15/22 (68.2)                           |
| Normal CSF findings            | 2/58 (3.4)                             |

CSF, cerebrospinal fluid; ICP, intracranial pressure; CEA, carcinoembryonic antigen

**Table 3.** Treatment of LM

| Treatment modality                     | Number of patients n (%) |
|----------------------------------------|--------------------------|
| Supportive care only                   | 5 (8.6)                  |
| IT CTx                                 | 43 (74.1)                |
| MTX                                    | 40 (93.0)                |
| MTX+cyclophosphamide                   | 3 (7.0)                  |
| RTx for LM                             | 17 (29.3)                |
| Whole brain                            | 13                       |
| Cerebellium                            | 1                        |
| Whole spine                            | 1                        |
| C-spine                                | 1                        |
| L-spine                                | 1                        |
| Systemic CTx                           | 24 (41.4)                |
| Conventional CTx                       | 18 (75.0)                |
| Targeted agents containing CTx         | 6 (25.0)                 |
| IT CTx alone                           | 18 (31.0)                |
| RTx alone                              | 5 (8.6)                  |
| Systemic CTx alone                     | 2 (3.5)                  |
| IT CTx+systemic CTx                    | 16 (27.6)                |
| IT CTx+RTx                             | 6 (10.3)                 |
| IT+systemic CTx                        | 3 (5.2)                  |
| IT CTx+RTx+systemic CTx                | 3 (5.2)                  |

LM, leptomeningeal metastasis; IT, intrathecal; CTx, chemotherapy; MTX, methotrexate; RTx, radiotherapy

**Fig. 1.** Kaplan-Meier curve of survival since the diagnosis of LM. LM, leptomeningeal metastasis; CI, confidence interval.
DISCUSSION

LM is mostly presented at the late stage of advanced solid tumors in the setting of widespread metastasis [3]. LM is associated with rapid and progressive neurological deterioration, and the major purpose of treatment for LM is palliation to improve neurologic deficits and the quality of life. Although the recent advances in systemic treatment of advanced cancers have resulted in significant improvements in survival, the prognosis of patients with LM remains poor. In this study, the median survival was only 2.4 months (95% CI, 1.0–3.7) in 58 patients with solid tumor who were diagnosed with LM, which is similar to previous reports of LM in patients with solid tumors (1.5 to 4.4 months) [6,11,12]. A good PS, systemic chemotherapy after LM diagnosis, and a prior history of brain radiation were associated good survival in our patients.

In general, breast cancer, lung cancer, and melanoma are associated with a high risk of LM development in patients with advanced solid tumors [3,4]. However, in studies on LM from Asian countries, melanomas were rare, and gastric cancer was one of the most common origins of LM in Asia including Korea. [6,11,12]. In this study, consistent with these Asian reports, breast cancer (39.7%), lung cancer (including NSCLC and small cell lung cancer, 22.4%), and gastric cancer (25.9%) were common causes of LM, and melanoma was reported in only one case. This study included patients with solid tumors that rarely cause LM, such as cervical cancer, ovarian cancer, esophageal cancer, and pancreatic cancer.

The detection of malignant cells in the CSF is the gold standard for LM, but the sensitivity of cytology is only 50% to 80% [13,14]. However, if malignant cell are not seen in the CSF, the analysis of CSF parameters such as opening pressure, cell counts, total protein levels, and glucose levels is helpful in diagnosing LM. The abnormal CSF findings suggesting LM include a high opening pressure (38–50%), elevated cell counts (46–64%), el-

| Table 4. Prognostic factor analysis for survival in patients with LM (continued) |
| Parameter | Media OS (months) | Univariate p value | Multivariate HR (95% CI) p value |
|-----------|------------------|--------------------|----------------------------------|
| IT chemotherapy | 0.971 | Yes | 2.7 |
| No | 2.1 |
| Systemic chemotherapy | 0.001 | 0.338 | 0.02 |
| (0.171–0.669) | Yes | 5.2 |
| No | 2.4 |

OS, overall survival; CI, confidence interval; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; PS, performance status; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; LM, leptomeningeal metastasis; IT, intrathecal
Elevated protein levels in the CSF, mainly as a result of the blood-brain barrier (BBB) breakdown, was a negative prognostic factor in previous studies [15,16], but our study did not show an association between a high protein level in the CSF and poor survival in patients with LM.

PS is one of the most important prognostic factors in patients with LM [6,8,11,15-17]. Consistent with other studies, patients with good PS (ECOG PS ≤2) in our study showed prolonged survival. Patients with good PS could be offered aggressive treatments for LM that include not only symptomatic management but also active anti-cancer chemotherapy. Waki et al. [6] reported that 58% of patients with PS 0–1 received IT chemotherapy, whereas only 27% of patients with PS 2–4 received treatment. In a small comparative study to determine the effect of IT chemotherapy according to the PS in patients with LM, IT chemotherapy was found to be more beneficial in patients with a good PS than in those with a poor PS (survival, 15.5 weeks vs. 6.0 weeks, p<0.01) [18].

Unfortunately, there is no standard treatment for LM due to the lack of randomized clinical trial data and the low incidence rate of LM. IT chemotherapy is a commonly used treatment modality for LM because drugs can be delivered directly into the CSF [3]. However, it's superiority compared with systemic chemotherapy has not been established in randomized trials. Our study showed that IT chemotherapy was not associated with prolonged survival, but systemic chemotherapy was an independent prognostic factor for survival. Systemic chemotherapy is not considered an effective treatment for LM, because most chemotherapeutic agents do not penetrate an intact BBB, and cannot reach the CSF in sufficient concentration [3]. However, the BBB may be disrupted by leptomeningeal involvement of the tumor, due to which, drugs could penetrate into the central nerve system [19]. In a randomized study to compare IT chemotherapy to systemic chemotherapy for LM in patients with breast cancer, the median survival was 18.3 weeks in the IT chemotherapy arm and 30.3 weeks in the systemic chemotherapy arm (although there was no statistical significance), and neurological complications were common in the IT chemotherapy arm (47% vs. 6%, p=0.0072) [20]. Several retrospective studies that analyzed the outcomes of LM showed that administration of systemic chemotherapy was associated with a prolonged survival [8,11,12,17]. Systemic chemotherapy could allow the simultaneous treatment of active systemic and leptomeningeal lesions. Recently, molecular targeted agents, such as epidermal growth factor receptor (EGFR)-targeted tyrosin kinase inhibitors (TKIs) (erlotinib or gefitinib) for NSCLC, have been used for LM treatment, and have shown promising results [21]. In a study by Liao et al. [22], EGFR-mutated NSCLC patients who were administered EGFR-TKIs for LM showed longer survival than patients who did not receive such treatment (10.9 months vs. 2.3 months, p<0.001). Although further randomized trials are needed, systemic chemotherapy, including newly developed molecular targeted agents, is an important therapeutic option for improving survival of selected patients with solid tumors who developed LM.

Our study has several limitations. First, this study has a retrospective design, and all data were only collected by review of medical records. Therefore, it was difficult to obtain information on the severity of symptoms at the time of LM diagnosis, and the improvement in the neurological deficit after treatment. Second, due to the small sample size and the heterogeneity of patients, the results of our analysis of prognostic factors for survival should be interpreted with caution. Although a history of brain radiation before LM diagnosis was associated with prolonged survival in our patients, the results have not been reported previously, and it is unclear whether such a history is a meaningful prognostic factor.

In conclusion, the outcome of LM in patients with solid tumors is poor; the median OS was less than 3 months in this
Nevertheless, a good PS at the time of LM and administration of systemic chemotherapy after LM diagnosis were positive prognostic factors for survival, consistent with previous studies. A prior history of brain radiation was also associated with prolonged survival, but it must be interpreted with caution. Although optimal treatment for LM remains challenging, systemic chemotherapy should be considered in selected patients, especially with a good PS and chemotherapy-sensitive diseases. Further studies to improve outcomes of LM are needed.

### Conflicts of Interest

The authors have no financial conflicts of interest.

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