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Survival Outcomes and Predictors for Recurrence of Surgically Treated Brain Metastasis From Non-Small Cell Lung Cancer

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Background There are numerous factors to consider in deciding whether to undergo surgical treatment for brain metastasis from lung cancer. Herein, we aimed to analyze the survival outcome and predictors of recurrence of surgically treated brain metastasis from non-small cell lung cancer (NSCLC).

Methods A total of 197 patients with brain metastasis from NSCLC who underwent microsurgery were included in this study.

Results A total of 114 (57.9%) male and 83 (42.1%) female patients with a median age of 59 years (range, 27–79) was included in this study. The median follow-up period was 22.7 (range, 1–126) months. The 1-year and 2-year overall survival (OS) rates of patients with brain metastasis secondary to NSCLC were 59% and 43%, respectively. The 6-month and 1-year progression-free survival (PFS) rates of local recurrence were 80% and 73%, respectively, whereas those of distant recurrence were 84% and 63%, respectively. *En-bloc* resection of tumor resulted in better PFS for local recurrence (1-year PFS: 79% vs. 62%, p=0.02). Ventricular opening and direct contact between the tumor and the subarachnoid space were not associated with distal recurrence and leptomeningeal seeding. The difference in PFS of local recurrence according to adjuvant resection bed irradiation was not significant. Moreover, postoperative whole-brain irradiation did not show a significant difference in PFS of distant recurrence. In multivariate analysis, only *en-bloc* resection was a favorable prognostic factor for local recurrence. Contrastingly, multiple metastasis was a poor prognostic factor for distant recurrence.

Conclusion *En-bloc* resection may reduce local recurrence after surgical resection. Ventricular opening and contact between the tumor and subarachnoid space did not show a statistically significant result for distant recurrence and leptomeningeal seeding. Multiple metastasis was only meaningful factor for distant recurrence.

Keywords Lung cancer; Brain metastases; Surgery; Recurrence; Survival.

INTRODUCTION

Lung cancer is the most common cause of cancer-related deaths in South Korea [1]. Brain metastasis is a complication and a major concern in the treatment of lung cancer. In fact, in some instances, lung cancer is retrospectively diagnosed in patients presenting with a brain metastatic mass. From a previous report, the incidence of brain metastasis in patients with primary lung cancer was 20% [2]. Additionally, it has been reported that the incidence of lung cancer with brain metastasis has been increasing in recent years, which places a great burden on public health services [3]. The treatment options for brain metastasis from primary lung cancer are surgery, conventional radiation therapy, systemic chemotherapy, and stereotactic radiosurgery (SRS). Recently, SRS, including

Gamma-Knife (GK) and Cyber-Knife (CK) radiosurgery (RS), has shown good results for the local control of single and multiple brain metastases. However, surgical resection continues to play an important role. Surgery provides immediate relief of mass effect and enables histopathologic examination of the obtained tissue from the procedure. Surgical resection is the essential treatment in large metastasis. However, there are numerous factors to consider in deciding whether patients with brain metastasis from lung cancer should undergo surgical treatment. These factors include current disease state of lung cancer, performance status, tolerability for general anesthesia and craniotomy, expected survival rate after surgery, and postoperative neurological deficits. According to previously published studies, the median survival of patients with lung cancer with brain metastasis was 3−12 months [4-7]. Considering the short survival and the quality of life of patients with cancer, prediction of recurrence and survival is important during surgical decision-making. From a neurosurgeon's perspective, minimizing local and distant brain recurrence after surgery of metastatic tumor is the critical consideration. Moreover, the need for adjuvant treatment after total resection of the metastatic tumor should also be considered. Herein, we aimed to determine the predictors of recurrence and survival outcomes of patients who were surgically treated for brain metastasis arising from non-small cell lung cancer (NSCLC).

MATERIALS AND METHODS

Patient selection

This retrospective study was approved by the Institutional Review Board of Asan Medical Center (approval No.: 2020-0466) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The need for informed consent was waived due to the retrospective nature of the study. Our institutional database was searched for diagnoses of metastatic brain tumors from lung cancer between January 2010 and December 2020. Only patients with brain metastasis from NSCLC who did not undergo surgical resection and those with brain metastasis from NSCLC who underwent microsurgery at our institute were enrolled in the current study. Recurrent tumors with no available information and brain metastasis from small cell lung cancer and other primary tumors were excluded. Altogether, 197 patients were included in this study. The inclusion criteria were as follows: 1) patients with metastatic brain tumors from NSCLC, 2) brain metastasis from NSCLC was treated by surgical resection, and 3) brain metastasis from NSCLC was confirmed via histopathological examination. The tumor size was defined by its maximal diameter in two dimensions.

Treatment and follow-up

The treatment decision for metastatic brain cancer from NSCLC was established in the integrated lung cancer treatment team. This team consisted of oncologists, radiation-oncologists, and neurosurgeons. The extent of resection in our study was re-defined as follows: gross total resection, complete removal of the tumor as indicated on postoperative MRI, subtotal resection, any incomplete resection of the tumor with less than 10% of the tumor visible as a remnant on postoperative MRI. The surgical methodology is classified as "*en-bloc* resection" and "piecemeal resection." The definition of "*en-bloc* resection" is removal of the entirely of a tumor without violating tumor capsule and the definition of "piecemeal resection" is removal of the tumor divided into small pieces.

SRS, including GKRS and CKRS, were additionally performed for residual tumors. GKRS was performed using a Leksell GK perfexion (Elekta, Stockholm, Sweden) from December 2011 until the present. Dose planning for the GKRS treatment involved MRI analysis in the Leksell gamma plan. The marginal prescription doses ranged from 20 Gy to 24 Gy. The Robotic Radiosurgery System Version 9.0 (Accuray, Sunnyvale, CA, USA) was used for CK treatments. For CK planning, CT images with a very thin slice (0.625-mm thickness with no slice gap) were obtained and fused with gadolinium-enhanced axial and coronal three-dimensional T1-magnetization-prepared rapid acquisition gradient-echo MR images (1.0-mm slice) in the Accuray MultiPlan system (version 4.5; Accuray). The median prescription dose was 35 Gy (range, 25−41 Gy). The dose was administered in three or five daily fractions. Conventional radiation therapy was administered for the surgical cavity or whole brain, the prescription dose was 30 Gy, which was fractionated by 2 Gy or 3 Gy.

Initial follow-ups involved clinical evaluation and an MRI in the immediate postoperative period (within 48 h), at the first and third months, and every 3 months thereafter.

Statistical analyses

The overall survival (OS), progression-free survival (PFS), and prognostic factors were evaluated. The OS and PFS outcomes were analyzed using the Kaplan-Meier survival analysis, and subgroup comparisons were performed using the log-rank tests. Potential prognostic factors for PFS, including age, sex, multiple metastases, adjuvant resection bed irradiation, adjuvant whole-brain radiation therapy (WBRT), period from lung cancer diagnosis to the occurrence of brain metastasis, postoperative neurological deficits, and immunohistochemical findings in NSCLC, were analyzed using the Cox-proportional hazards model. The proportional hazards assumption was confirmed via testing of the Schoenfeld residuals, and no relevant violations were found. All statistical analyses were conducted using the SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA). A *p*-value <0.05 was considered statistically significant.

RESULTS

Study patient characteristics and treatment outcomes

There were 114 (57.9%) male and 83 (42.1%) female patients with a median age of 59 years (range, 27–79 years). The most common type of NSCLC among the participants was adenocarcinoma (145 participants, 73.6%). Among the participants, 52.3% had epidermal growth factor receptor (*EGFR*) mutation, whereas 47.7% had none. The most common initial lung cancer stage was stage IV (107, 54.3%). The most common location was the frontal lobe (33%), which was followed by the parietal lobe, cerebellum, and the temporal lobe. The representative image findings are presented in Fig. 1. A total of 148 patients (75.1%) harbored single brain metastasis, while 49 (24.9) had multiple brain metastasis. In patients with multiple metastasis, the largest brain tumor was resected, while the other tumors were treated via SRS and radiotherapy. The median period from lung cancer diagnosis to the occurrence of brain metastasis was 21 months (range, 0–226 months). A total of 56 patients (28.4%) had extracranial metastasis. Among the patients, 12.7% of patients had a diagnosis-specific graded prognostic assessment (DS-GPA) score of 0.0–2.0, 50.8% had a DS-GPA score of 2.5–3.0, and 36.5% had a DS-GPA score of 3.5–4.0. There were 38 patients who received previous irradiation for brain metastatic tumor. The median size of tumor was 41.5 mm (range, 10–72 mm). A total of 190 patients (96.4%) underwent total resection of the tumor. Intraoperatively, *en-bloc* resection was performed in 119 patients (60.4%), while piecemeal resection was performed in 78 (39.6%). Ventricular opening was performed in 38 patients (19.3%). Direct contact of the tumor with the subarachnoid space, protrusion through the cortex and cisternal space, and adherence to dura were noted in 101 patients (51.3%). Postoperative com-

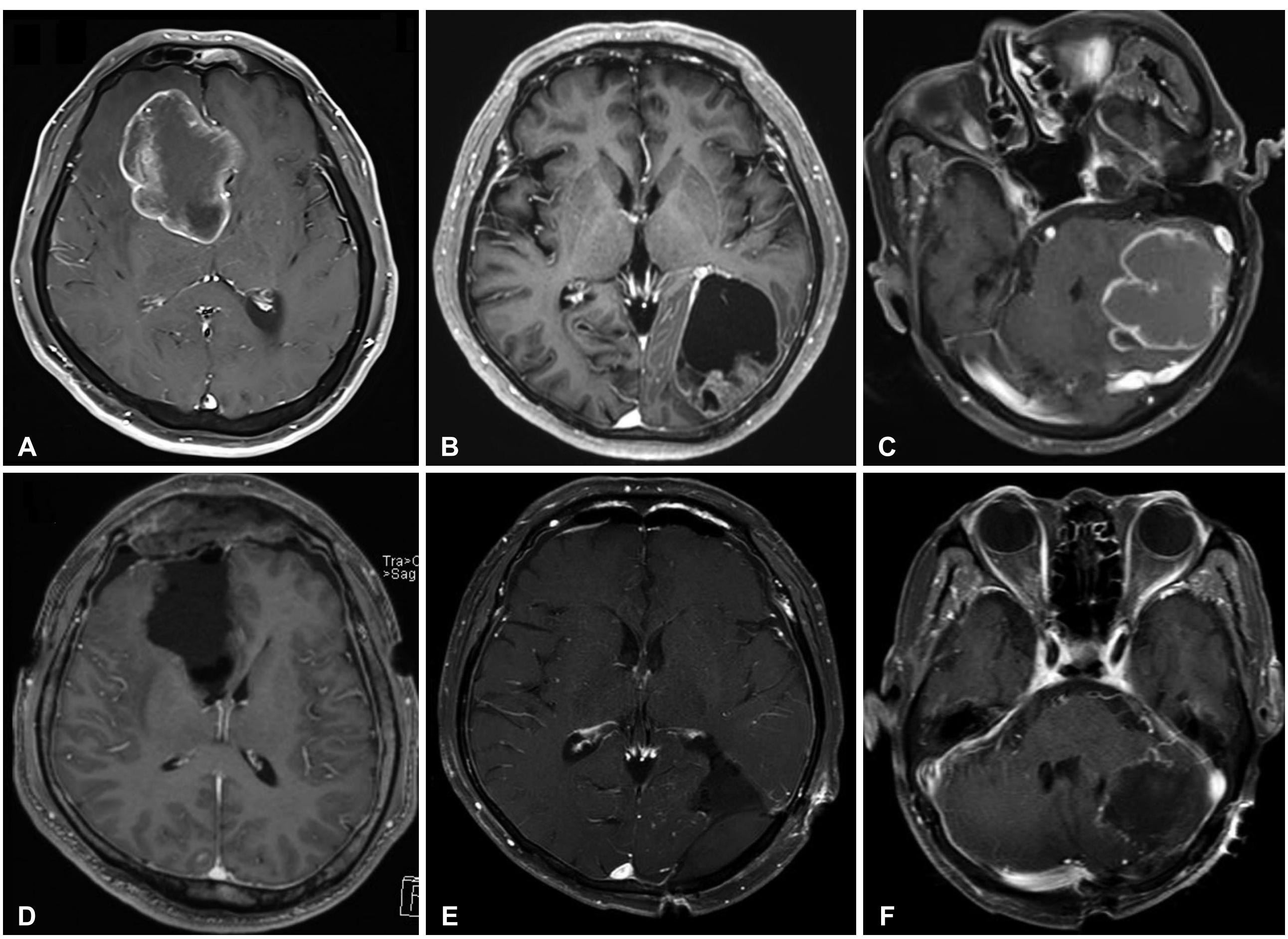

Fig. 1. Representative radiological findings for brain metastasis from lung cancer. A and D: A 52-year-old male patient with non-small cell lung cancer (NSCLC)-squamous cell carcinoma. A large right frontal lobe tumor was resected to relieve intracranial hypertension. Other lesions were treated by gamma knife radiosurgery. B and E: A 70-year-old male patient with NSCLC adenocarcinoma. The single left occipital solid and the cystic tumor were resected. Postoperative homonymous hemianopsia occurred. The patient did not receive adjuvant therapy. C and F: A 79-year-old male patient with NSCLC squamous cell carcinoma. A large cystic cerebellar tumor was resected to relieve obstructive hydrocephalus. Postoperatively, the fourth ventricle was decompressed, and the hydrocephalus was relieved.

Table 1. The basal characteristics of the enrolled patients

Characteristics	Value (n=197)
Age (yr)	59 [27–79]
Sex	
Male	114 (57.9)
Female	83 (42.1)
Histology	
NSCLC	
Squamous	37 (18.8)
Adenocarcinoma	145 (73.6)
Others	15 (7.5)
EGFR mutant	104 (52.3)
EGFR non-mutant	93 (47.7)
Initial lung cancer stage at diagnosis NSCLC	
I	33 (16.7)
II	15 (7.6)
III	41 (20.8)
IV	107 (54.3)
Location of tumor	
Frontal	65 (33.0)
Parietal	53 (26.9)
Temporal	29 (14.7)
Occipital	17 (8.6)
Cerebellum	31 (15.7)
Others	1 (0.5)
Single brain metastasis	148 (75.1)
Multiple brain metastasis	49 (24.9)
Period from lung cancer diagnosis to brain metastasis (mo)	21 [0–226]
Extracranial metastasis	
Absence	141 (71.6)
Presence	56 (28.4)
DS-GPA score	
0.0–2.0	25 (12.7)
2.5–3.0	100 (50.8)
3.5–4.0	72 (36.5)
Previous irradiation history (SRS or radiotherapy)	38 (19.3)
Size of tumor (mm)	41.5 [10–72]
Extent of resection	
Total resection	190 (96.4)
Subtotal resection	7 (3.6)
Intraoperative findings	
En-bloc resection	119 (60.4)
Piecemeal resection	78 (39.6)
Intraoperative ventricle opening	38 (19.3)
Direct contact with subarachnoid space	101 (51.3)
Postoperative complication	11 (5.6)
ICH	5
EDH	3
Infarction	4
Postoperative newly developed neurological deficits	13 (6.6)
Adjuvant radiotherapy	
Resection bed	63 (32.0)
Whole brain	25 (12.7)
Adjuvant chemotherapy	
Non-target agents	84 (42.6)
Target agents	69 (35.0)
Follow-up period (mo)	22.7 [1–126]

Values are presented as median [range], n (%), or n. NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; SRS, stereotactic radiosurgery; EDH, epidural hemorrhage; ICH, intracerebral hemorrhage; KPS, Karnofsky Performance Scale; DS-GPA, disease-specific graded prognostic assessment

plication occurred in 11 patients (5.6%), and newly developed neurological deficits was noted in 13 patients (6.6%).

Adjuvant resection bed irradiation was performed in 63 patients (32%), while whole brain irradiation was performed in 25 patients (12.7%). Target agent chemotherapy was done in 69 patients (35%), while non-target agent chemotherapy was done in 84 patients (42.6%). The median follow-up period was 22.7 months (range, 1–126 months). The detailed characteristics of enrolled patients are presented in Table 1.

PFS and OS between groups

The 1-year and 2-year OS rates of patients with brain metastasis from lung cancer were 59% and 43%, respectively. The 6-month and 1-year PFS of local recurrence were 80% and 73%, respectively, while those of distant recurrence were 84% and 63%, respectively (Fig. 2).

Intraoperative findings: *en-bloc* resection and piecemeal resection

En-bloc resection of tumor resulted in a better PFS for local recurrence (1-year PFS: 79% vs. 62%, p=0.02) and for distant recurrence (1-year PFS: 69% vs. 54%, p=0.06). The PFS for distant recurrence, however, showed a marginal statistical significance (Fig. 3).

Intraoperative findings: ventricle opening and tumor contact subarachnoid space

Ventricular opening during surgery was not associated with distal recurrence and leptomeningeal seeding. In addition, tumors that were in direct contact with the subarachnoid space were not associated with distant recurrence and leptomeningeal seeding (Fig. 4).

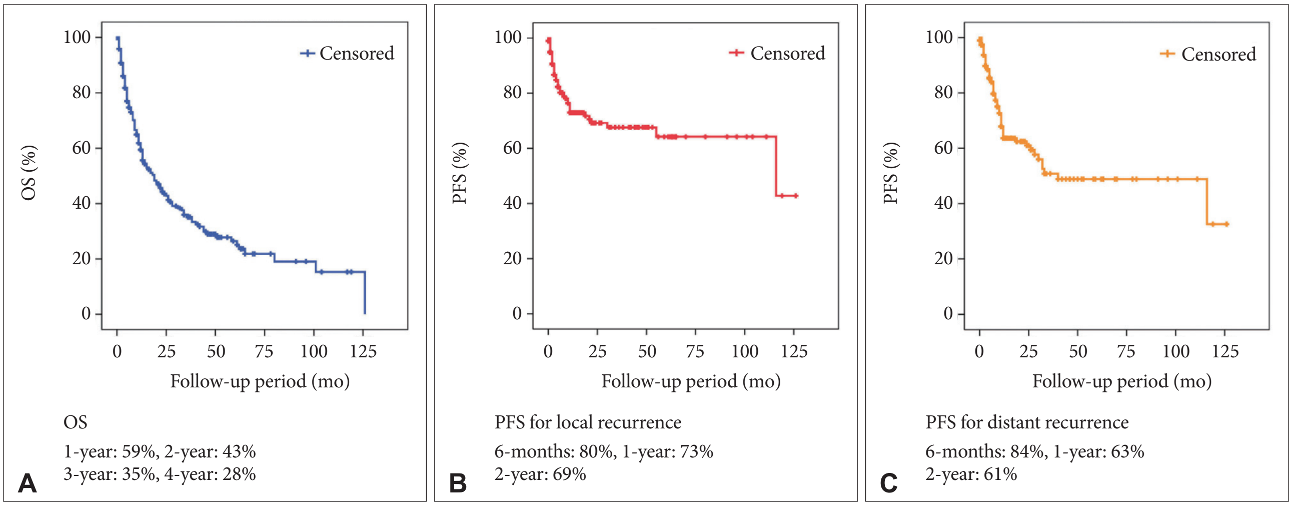

Fig. 2. Kaplan-Meier survival analysis of the enrolled patients. A: Overall survival (OS) of all patients with brain metastasis from non-small cell lung cancer (NSCLC). B: Progression-free survival (PFS) of local recurrence of all the surgically treated patients with NSCLC brain metastasis. C: PFS of distant recurrence of all the surgically treated patients with NSCLC brain metastasis.

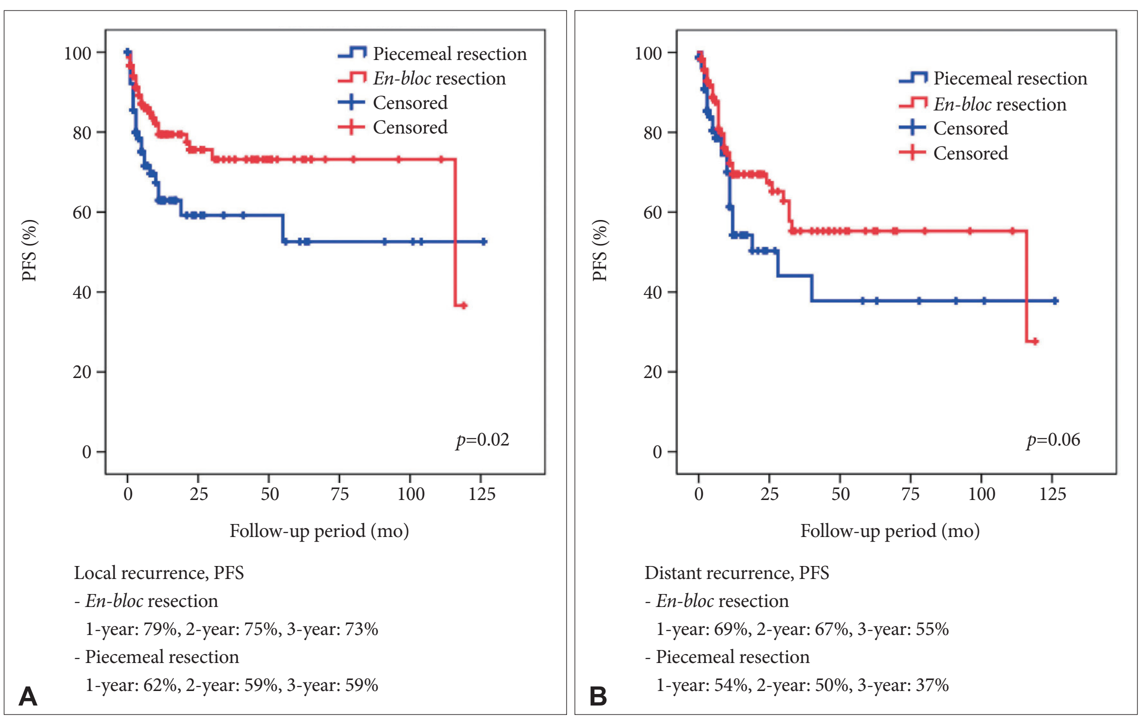

Fig. 3. The Kaplan-Meier survival analysis of the enrolled patients. A: The difference of the progression-free survival (PFS) for local recurrence for *en-bloc* resection and piecemeal resection in the NSCLC group. The difference was statistically significant (*p*=0.02). B: The difference of PFS for distant recurrence for *en-bloc* resection and piecemeal resection in the NSCLC group. The difference showed marginal statistical significance (*p*=0.06).

Adjuvant resection bed irradiation and WBRT

The difference of PFS of local recurrence according to adjuvant resection bed irradiation was not significant (1-year: 69% vs. 79%, 2-year: 67% vs. 67%; *p*=0.3). Whole-brain irradiation did not show a significant difference in PFS of distant recurrence (1-year: 63% vs. 66%, *p*=0.68) (Fig. 5).

Prognostic indicators of PFS and OS

We determined and analyzed the possible predictors of local and distant recurrence and OS, including age, sex, multiple metastases, previous irradiation history, history of *en-bloc* resection, presence of an intraoperative ventricular opening, direct contact of the tumor with the cerebrospinal fluid space, history of resection bed irradiation, history of WBRT, presence of postoperative neurological deficits, presence of extracranial metastasis, and immunohistochemical findings (*EGFR* mutation, *ALK-1* mutation, and *PD-L1* mutation).

In the univariate analysis, previous irradiation was found to be a poor prognostic factor for local recurrence (hazard ratio [HR]=1.8 [95% confidence interval, CI: 1.00–3.40], p=0.05), while a history of *en-bloc* resection was found to be a favorable prognostic factor for local recurrence (HR=0.52 [95% CI: 0.30–0.91], p=0.02). Multiple metastasis was a poor prognos-

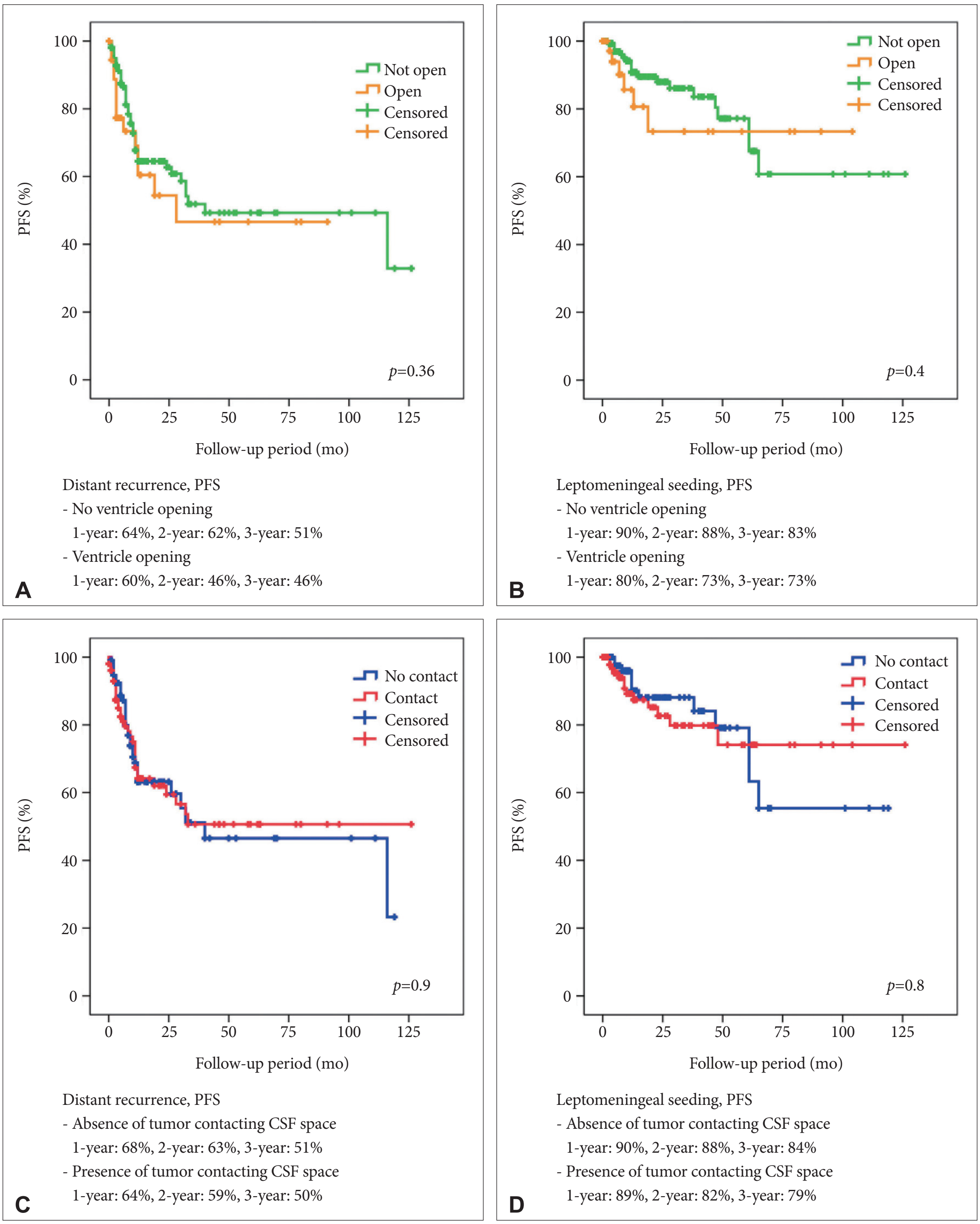

Fig. 4. The Kaplan-Meier survival analysis of the enrolled patients. A: Progression-free survival (PFS) difference for distant recurrence according to intraoperative ventricle opening. There was no significant difference in PFS for distant recurrence. B: PFS difference for leptomeningeal seeding according to intraoperative ventricle opening. There was no significant difference in PFS for leptomeningeal seeding. C: PFS difference for distant recurrence according to tumor contacting cerebrospinal fluid (CSF) space. There was no significant difference in PFS for distant recurrence. D: PFS difference for leptomeningeal seeding according to tumor contacting CSF space. There was no significant difference in PFS for leptomeningeal seeding.

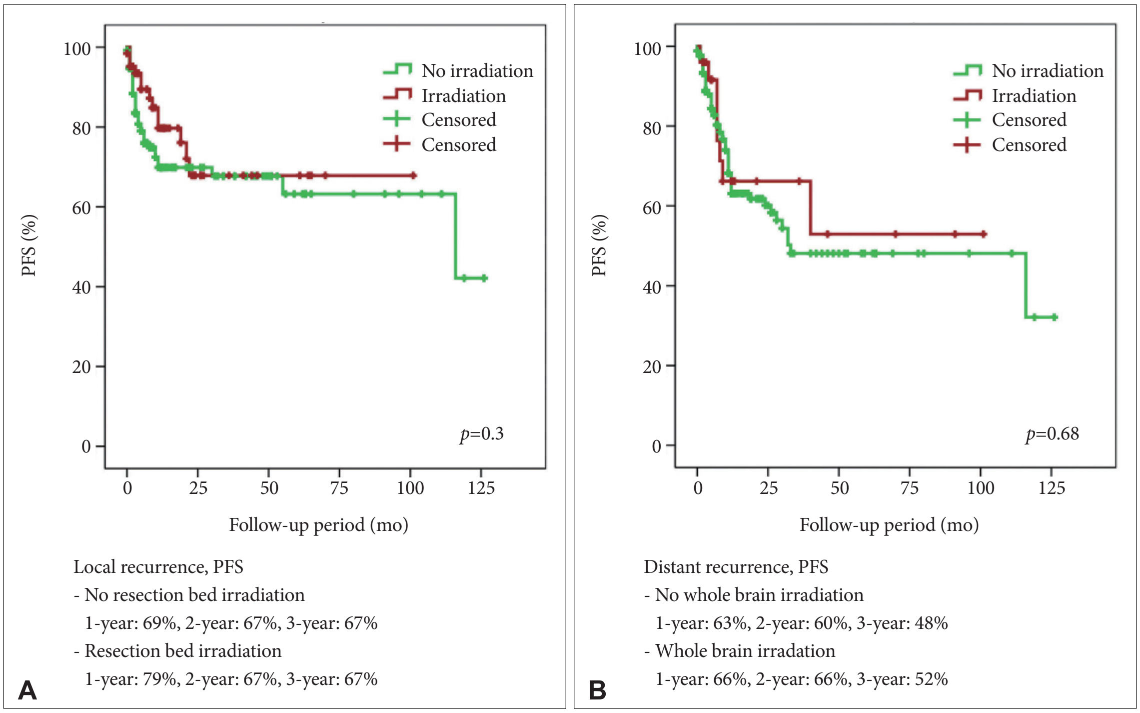

Fig. 5. The Kaplan-Meier survival analysis of the enrolled patients. A: Progression-free survival (PFS) for local recurrence according to the resection bed irradiation. There was no significant difference in PFS for local recurrence. B: PFS for distantl recurrence according to the whole brain irradiation. There was no significant difference in PFS for distant recurrence.

tic factor for distant recurrence (HR=2.00 [95% CI:1.17–3.42], *p*=0.01). The female sex and the presence of *EGFR* mutation were favorable prognostic factors for OS (HR=0.52 [95% CI: 0.36–0.75], *p*=0.01 and HR=0.62 [95% CI: 0.42–0.93], *p*=0.02, respectively). Postoperative neurological deficits and extracranial metastasis were poor prognostic factors for OS (HR=2.57 [95% CI: 1.29–5.14], *p*=0.01 and HR=1.58 [95% CI: 1.09–2.29], *p*=0.01). However, postoperative usage of chemotherapeutic agent (including conventional agent and molecular target agent) did not affect the local recurrence, distant recurrence, and OS. In multivariate analysis, only *en-bloc* resection was a favorable prognostic factors for local recurrence (HR=0.52 [95% CI: 0.30–0.91], *p*=0.02). Multiple metastasis was a poor prognostic factor for distant recurrence (HR=2.2 [95% CI: 1.31–3.95], *p*=0.01). In terms of OS, female sex was only the favorable prognostic factor (HR=0.61 [95% CI: 0.38–0.97], *p*=0.03), while extracranial metastasis was identified as a poor prognostic factor (HR=1.64 [95% CI: 1.42–1.97], *p*=0.04). The detailed analysis is presented in Table 2.

DISCUSSION

Lung cancer is the most frequent source of metastatic brain tumors. It occurs in 17%–65% of patients with primary lung cancer [3,8]. The rate of lung cancer brain metastasis has been increasing in recent years [3]. According to previously published studies, the prognosis for patients with metastatic brain cancer from lung cancer is poor, with the median OS reported to be 1 to 12 months despite treatment [4-6]. However, there are significant advances in the management of lung cancer. In our study, the median OS was over 12 months.

To prolong the life and improve the quality of life of patients with metastatic brain cancer from lung cancer, there should be relief of neurological symptoms and intracranial hypertension. The treatment of brain metastasis is critical in patients with lung cancer. Thus, the role of neurosurgeons is considerably important in the treatment of brain metastasis from lung cancer. From the perspective of a neurosurgeon in brain metastasis treatment, decreasing local and distant recurrence while maintaining or improving the quality of life of patients are the most important considerations. Surgery, SRS, conventional radiation therapy, and systemic chemotherapy are the possible treatment strategies in brain metastasis. The efficacy of radiosurgery for small-sized multiple brain metastasis has been proven [7]. Moreover, Chon et al. [9] reported the feasibility of fractionated radiosurgery for medium-sized brain metastasis. For medium to large tumors, surgical resection is still an essential tool. However, surgery is the only option for large tumors with mass effects, which should be confirmed pathologically. In these cases, progression has been observed even after radiosurgery or radiotherapy. In our center, decision of surgical treatment of BM has been established after multi-

Table 2. An analysis of the predictors of prognosis of surgically resected brain metastasis from lung cancer using the Cox-proportional hazard analysis

	Univariate analysis						Multivariate analysis					
	PFS (local recur)		PFS (distant recur)		Overall survival		PFS (local recur)		PFS (distant recur)		Overall survival	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age >70 years	NA		NA		1.15 (0.71–1.85)	0.56	NA		NA		NA	
Sex, female	NA		NA		0.52 (0.36–0.75)	0.01	NA		NA		0.61 (0.38–0.97)	0.03
Multiple metastasis	0.96 (0.50–1.84)	0.91	2.00 (1.17–3.42)	0.01	1.27 (0.85–1.90)	0.22	NA		2.2 (1.31–3.95)	0.01	NA	
Previous irradiation	1.8 (1.00–3.406)	0.05	0.69 (0.35–1.38)	0.30	1.02 (0.65–1.58)	0.93	0.60 (0.32–1.12)	0.11	NA		NA	
En-bloc resection	0.52 (0.30–0.91)	0.02	0.63 (0.38–1.04)	0.07	0.82 (0.57–1.17)	0.28	0.52 (0.30–0.91)	0.02	1.8 (1.0–3.06)	0.20	NA	
Ventricle opening	1.20 (0.60–2.42)	0.59	1.30 (0.72–2.37)	0.37	1.35 (0.88–2.06)	0.15						
Direct contact with CSF space	1.31 (0.75–2.30)	0.33	1.00 (0.61–1.64)	0.98	0.96 (0.67–1.37)	0.83						
Adjuvant resection bed irradiation	0.72 (0.38–1.36)	0.31	NA		1.08 (0.74–1.57)	0.67	NA		NA		NA	
Adjuvant WBRT	NA		0.86 (0.41–1.80)	0.69	0.96 (0.56–1.63)	0.88	NA		NA		NA	
DS-GPA score	NA		NA				NA		NA			
2.5–3.0					1.81 (0.93–3.51)	0.07					0.79 (0.37–1.69)	0.55
3.5–4.0					1.65 (0.82–3.29)	0.15					0.96 (0.62–1.49)	0.88
Postoperative neurological deficits	NA		NA		2.57 (1.29–5.14)	0.01	NA		NA		0.73 (0.29–1.81)	0.51
Extracranial metastasis	NA		NA		1.58 (1.09–2.29)	0.01	NA		NA		1.64 (1.42–1.97)	0.04
EGFR mutant	1.1 (0.60–2.66)	0.93	1.47 (0.85–2.55)	0.16	0.62 (0.42–0.93)	0.02	NA		0.37 (0.04–2.80)	0.30	1437.81 (0.00–1.117E53)	0.90
ALK mutant	0.91 (0.21–2.59)	0.86	0.70 (0.28–1.78)	0.46	0.98 (0.52–1.86)	0.96			NA		NA	
PD-L1 positive	1.15 (0.40–3.34)	0.78	1.52 (0.54–4.26)	0.41	1.98 (0.84–4.64)	0.11			NA			
Chemotherapy												
None												
Non-target agents	0.38 (0.12–1.17)	0.09	0.64 (0.23–1.78)	0.39	0.38 (0.10–1.43)	0.15						
Target agents*	0.72 (0.25–2.03)	0.98	0.83 (0.30–2.32)	0.73	1.16 (0.3–3.86)	0.80						

*Target agents: molecular target agents. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; WBRT, whole brain radiation therapy; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, programmed death ligand-1 disciplinary discussion between the neurosurgeons, radiation-oncologists and medical oncologists. Generally, SRS including GKRS or CKRS, are considered primarily for small tumor. In medium sized tumor, SRS is primarily considered for tumor which do not show mass effect, deep or eloquent location tumor. However, surgical resection is primarily considered for large tumor or rapid alleviating neurological symptom or tissue histopathological examination. Recently, we performed surgical resection in patients with single metastasis and multiple metastases. Surgery with adjunctive radiosurgery or radiotherapy were performed to prolong the life and to relieve symptoms related to brain metastasis.

In this study, we focused on analyzing possible predictors for local and distant recurrence of brain metastatic tumors from NSCLC from a neurosurgeon's perspective. Total resection of metastatic brain tumor was performed in 97% of the patients. To reduce local recurrence, *en-bloc* resection was performed. *En-bloc* resection resulted in better outcomes compared with those of piecemeal resection [10]. In our series, we did gross total resection without plus normal tissue resection. However, concordant with a previous report, *en-bloc* resection resulted in a better local control of NSCLC brain metastasis in our study. Furthermore, Yoo et al. [11] reported that a plus 5 mm adjacent white matter resection reduced local recurrence. *En-bloc* tumor resection usually involves tumor resection in the gliotic plane or normal white matter adjacent the tumor. Furthermore, we found that supra-marginal resection leads to less local recurrence after tumor resection. Although tumor resection was not feasible in all tumors, "*en-bloc*"-fashion resection plus white matter was pursued for non-eloquent area tumors to reduce the local recurrence rate. There has not been concrete evidence of impact of tumor cystic fluid for tumor recurrence or dissemination. However, in cystic metastatic tumor surgery, we performed cystic fluid aspiration before tumor resection to prevent rupture of tumor cyst. After cyst aspiration, it is not too difficult to perform extra-tumoral dissection and "*en-bloc*" resection. Theoretically, ventricular opening or direct contact between the tumor and the subarachnoid space, including cortically protruding tumor, protruding tumor into the cisternal space, and tumor adherent to the dura, may act as routes where the tumor may spread. In primary malignant brain tumors, ventricular opening during brain tumor resection increased the incidence of distant recurrence and leptomeningeal seeding [12]. However, in this study, ventricular opening during surgery and direct contact between the tumor and the subarachnoid space were not associated with distant recurrence and leptomeningeal seeding.

Postoperative irradiation, including SRS and conventional radiation therapy, could be applied in the resection cavity to reduce local recurrence. SRS and WBRT showed comparable results in terms of local recurrence in brain metastasis [6,13]. In a previous report, the efficacies of SRS and WBRT were comparable [6,13,14]. WBRT has been needed for disseminated metastasis and it has performed a unique role. However, considering the neuro-cognitive complications such as learning and memory dysfunction, SRS may be a more suitable tool for resection bed irradiation [15]. Theoretically, resection bed irradiation may provide good local control but poor distant recurrence control. However, in our series, resection bed radiotherapy and radiosurgery did not affect the local recurrence. In addition, postoperative WBRT did not affect the incidence of distant recurrence.

The results of our study should be cautiously interpreted. In this study, it was not implicated that adjuvant radiotherapy and radiosurgery might not have been mandatory after surgical resection for patients with metastatic brain cancer from NSCLC since our study did not follow a single treatment consensus and since the patients did not receive the same chemotherapeutic regimen. In the previous studies, only WBRT for brain metastasis influenced survival from 1 to 3 months [16,17]. Applying WBRT for reducing distant recurrence in lung cancer brain metastasis, considering its survival benefit and neurocognitive impairment, was still debatable. Although it should be cautiously interpreted, according to our result, WBRT did not improve the PFS for distant recurrence.

At our institute, there was no consensus for applying adjuvant radiotherapy or SRS. Instead, it depended on the opinion of individual oncologists. Standard cytotoxic chemotherapy used in lung cancer, mainly platinum agents, was not effective metastatic brain cancer from NSCLC due to poor penetration of the blood-brain barrier [4]. On the other hand, molecular-targeted therapy showed promising effects on patients with metastatic brain cancer from NSCLC [4,18]. *EGFR* mutation, *ALK* rearrangement, and *PD-L1* are targetable mutations. They have shown effectiveness in intracranial disease control. Moreover, a recent clinical trial reported promising results of *EGFR*-targeted therapy for leptomeningeal diseases [12]. However, *EGFR*-targeted therapy is not suitable for symptomatic and immediate life-threatening brain metastasis. Nevertheless, it could still be applied for small metastasis and disseminated disease. At our institute, we used a molecular-targeted agent after surgical resection of metastatic brain tumor according to the status of targetable gene mutation. We evaluated the difference of local recurrence and distant recurrence concerning *EGFR*, *ALK-1*, and *PD-L1* in the NSCLC group. There was no statistically significant difference in local and distant recurrence. Recently, molecular target agents have been shown the efficacy for control of brain metastatic tumors. However, there has been lack of studies for impact of molecular target agents for local or distant recurrence after surgery for brain metastasis [19]. The efficacy of molecular target agent after brain metastatic tumor resection should be evaluated in future studies.

In this study, only *en-bloc* resection affected the prognosis for local recurrence, while only multiple brain metastasis affected the prognosis for distant recurrence. In cases of multiple brain metastasis, short-term follow-up brain imaging was needed to detect another metastasis. In terms of OS, female sex and extracranial metastasis were statistically significant prognostic factors. Female sex was already known as a favorable prognostic factor of lung cancer [20].

The maintenance of the quality of life of patients with cancer is an important consideration. Considering the lower chance of cure of disease in patients with brain metastasis from lung cancer, the postoperative complication significantly impacting the performance status of patients should be minimized. In recent studies, the eloquent location of metastatic brain tumors could be managed using radiosurgery [7,9]. A declining performance status due to postoperative neurological deficits not only restricted further chemotherapy or radiation therapy but also led to other medical complications, which jeopardized the survival of patients with lung cancer. In our study, the postoperative complication group showed a significantly lower OS rate. We should minimize the postoperative complication in brain metastasis surgery and consider that the complication critically influences survival.

Our current study had some limitations. First, it was a retrospective investigation that included 197 patients with lung cancer brain metastasis. Along with the limitations inherent to any retrospective design, this precluded less meaningful multivariate analysis of survival outcomes or predictors of local and distant recurrence. Moreover, this study series spanned around 10 years; therefore, the treatment methods varied. The management strategy of lung cancer brain metastasis varied according to individual neurosurgeons, which made it challenging to conclude on the optimal intervention strategies and outcomes in these cases. However, we believe that the data from our current single-center series make a valuable contribution to the available literature on these extremely rare tumors and to a future meta-analysis of this disease.

In summary, surgery of brain metastasis from NSCLC is an important treatment method to improve survival and defer life-threatening events during lung cancer treatment. *En-bloc* resection may reduce local recurrence after surgical resection of brain metastasis. Ventricular opening and contact between the tumor and subarachnoid space did not show a statistically significant result for distant recurrence and leptomeningeal seeding. Resection bed irradiation and WBRT did not show effectiveness to reduce local and distant recurrence. However, it should be cautiously interpreted. Multiple metastasis was only meaningful factor for distant recurrence. Future large-sized study should be conducted.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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