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The Efficacy of Postoperative Chemotherapy for Patients with Metastatic Brain Tumors from Non-Small Cell Lung Cancer

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Background The purpose of this study is to evaluate the effect of postoperative chemotherapy on recurrence and survival in patients after resection of metastatic brain tumors from non-small cell lung cancers.

Methods Patients who went through resection of a single metastatic brain tumor from non-small cell lung cancer from July 2001 to December 2012 were reviewed. Those selected were 77 patients who survived more than 3 months after surgery were selected. Among them, 44 patients received various postoperative systemic chemotherapies, 33 patients received postoperative adjuvant whole brain radiotherapy (WBRT). Local/distant recurrence rate, local/distant recurrence free survival, disease free survival (DFS), and overall survival were compared between the two groups.

Results Among the 77 patients, there were 19 (24.7%) local recurrences. Local recurrence occurred in 7 (21.2%) of 33 patients in the adjuvant radiotherapy (RT) group and in 12 (27.3%) of the 44 patients in the chemotherapy group (p=0.542). Among the 77 patients, there were 34 (44.1%) distant recurrences. Distant recurrence occurred in 7 (21.2%) of the 33 patients in the adjuvant RT group and in 27 (61.4%) of the 44 patients in the chemotherapy group (p<0.0005). Patients' survival in terms of local recurrence free survival, distant recurrence free survival, DFS, and overall survival was not shown to be statistically different between the two groups before and after adjusting for covariates.

Conclusion There was no significant difference observed between postoperative adjuvant chemotherapy and adjuvant WBRT in terms of patients' survival. Postoperative chemotherapy is more feasible and may be an appropriate option for simultaneous control of both primary and metastatic lesions.

Key Words Brain; Metastasis; Surgery; Chemotherapy; Radiotherapy; Survival; Recurrence.

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INTRODUCTION

Whole brain radiotherapy (WBRT) after resection of brain metastasis has been long considered as a standard treatment which is effective in achieving local disease control without survival prolongation, but it is frequently burdened with significant neurotoxic side effects [1]. In the presence of oligometastasis to the brain (one to three lesions), the treatment of choice may be radiosurgery or surgical removal, which is known to prolong survival [2]. However, the evidence on the efficacy of chemotherapy for brain metastasis is limited, with data reported in various studies showing response rates ranging from 15 to 30% [3]. The effect of systemic chemotherapy for brain metastasis has been believed to be limited due to the presence of blood brain barrier (BBB) [3,4]. However, BBB is known to be broken down in contrast enhancing lesions, and chemotherapeutic agents may cross the BBB in patients with established brain metastases as reported in some studies [4]. We hypothesized that microscopic remnant tumor cells after resection of a metastatic tumor may be controlled by systemic chemotherapy without WBRT. This retrospective analysis evaluated the therapeutic impact of the postoperative systemic chemotherapy after resection of met-

astatic brain tumors from non-small cell lung cancer (NSCLC) compared with WBRT. Surgical resection is the standard treatment modality for single, large, surgically accessible lesion; however, the reported local recurrence rate after metastatic brain tumor resection was significantly high, up to 34% [5]. Local recurrence after surgical resection is believed to develop from infiltrating remnant tumor cells [5]. To reduce local recurrence, we reported a novel surgical method referred to as microscopic total resection (MTR) [5]. The key feature of this method is to remove both the tumor and surrounding brain tissue until multiple margin biopsies are negative for cancer cells [5]. Through this technique, the local recurrence rate was reduced even without WBRT [5]. Previously, we also reported the therapeutic efficacy of frontline systemic chemotherapy for minimally symptomatic synchronous brain metastasis [4]. In our study, systemic chemotherapy group showed survival that was not inferior compared to the WBRT group, and, primary and metastatic brain tumors showed almost the same response rates. There was close correlation noted between intracranial and extracranial tumor responses. Moreover, the goal in the treatment of metastatic brain tumors should be simultaneous control of both brain and systemic disease, since about 70% of the patients die from primary disease progression. Also, recovery of neurologic deficits and preserving patients' qualities of life are important issues. In 2001, a French group reported the results of a phase III study on early versus delayed WBRT in patients with synchronous brain metastasis [6]. One hundred and seventy six patients were randomized to receive chemotherapy alone for at least the two first cycles, or chemotherapy and concurrent WBRT. The overall survival (OS) and progression free survival rates were similar in the two groups. The timing of brain radiotherapy (RT) did not have any effect on survival when the patients were treated with chemotherapy. They showed similar chemo-response between the cerebral and systemic lesions. In a recent review paper, the response rate of brain metastases from NSCLC to systemic chemotherapy have been reported to be up to 50% [3]. Primary and metastatic brain tumors showed similar chemo-sensitivities. There was close correlation between intracranial and extracranial tumor responses. Novel agents, such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors showed higher response rates up to 70−80% and longer progression free and OS in a subset of patients with EGFR mutations. Since most of clinical trials on these agents have excluded patients with brain metastasis, few prospective data are available on the effect of these agents in this setting. However, in recent years, several authors have reported a growing number of cases of partial and complete response in brain metastasis patients treated with EGFR tyrosine kinase inhibitor especially those with EGFR mutations [3,7-15]. The above findings stimulated us to evaluate the role of systemic chemotherapy as a postoperative adjuvant treatment in patients with brain metastases from NSCLC. We hypothesized that microscopic remnant tumor cells after resection of metastatic tumors may be controlled by systemic chemotherapy without WBRT. This retrospective analysis evaluates the therapeutic impact of the adjuvant systemic chemotherapy after resection of metastatic brain tumor from NSCLC compared with WBRT.

MATERIALS AND METHODS

Patient selection

Patients who underwent resection of a single metastatic brain tumor from non-small cell lung cancer from July 2001 to December 2012 were reviewed, and a total of 77 patients who survived more than 3 months after surgery and had at least one postoperative MRI follow-up were selected. Among them, 44 patients received postoperative adjuvant chemotherapy and 33 patients received postoperative adjuvant WBRT. Local/distant recurrence rates, local/distant recurrence free (DRF) survival, disease free survival (DFS), and OS were compared between two groups.

Data review

The patients' age, sex, disease types (adenocarcinoma, squamous cell carcinoma), tumor location (supratentorial, infratentorial), timing of metastasis (synchronous, metachronous), Karnofsky performance status (KPS) score, recursive partitioning analysis (RPA) class, administration of adjuvant radiation therapy, local and distant brain tumor recurrence, duration of follow-up, and survival time were retrospectively reviewed (Table 1).

Surgical technique: microscopic total resection

MTR is a surgical technique for metastatic brain tumors that was previously reported by our group [5]. In brief, after removal of metastatic brain tumor, we removed the surrounding brain tissue to a depth of 5 mm, and then performed multiple margin biopsies until negative tumor cells were confirmed pathologically. Additional removal was performed if biopsy results were tumor positive.

Adjuvant chemotherapy

Fourteen patients received chemotherapy based on irinotecan and cisplatin (IP), 10 based on gefitinib, 7 based on taxotere, and 6 based on gemcitabine. Other drugs included pemetrexate, methotrexate, etoposide, paclitaxel.

Adjuvant RT

Both whole-brain and partial brain radiation therapy was included in the adjuvant RT when it was administered postoperatively before the development of brain tumor recurrence. Whole-brain radiation therapy was administered as 30 Gy in 10−15 fractions. Partial brain radiation therapy was administered as 30 Gy in 5−10 fractions.

Postoperative follow-up

The absence of residual tumor was confirmed using MRI within 48 hours of surgery. Thereafter, all patients were followed up with brain MRI every 3 months or when clinically indicated. A local/distant recurrence was defined as a tumor recurrence at the original site of resection determined by follow-up MRI.

Statistical analysis

Differences in patients' characteristics between adjuvant RT first and chemotherapy first groups were tested using Pearson's chi-square test or Fisher's exact test for categorical variables, and Student's t-test for continuous variables. The primary endpoints of interest included local recurrence free (LRF) survival and OS. Patients who developed local brain tumor recurrence at the surgical site or distant recurrence at a distant site during the follow-up were counted and compared between the two groups. LRF survival time was defined as the time from the date of resection until local recurrence or death if the date of death was within 6 months from the last recurrence evaluation. Otherwise, it was censored at the time of last follow-up. DRF survival was defined similarly for distant recurrence. Local/distant recurrences or death was used for DFS in a similar manner. OS time is defined as time from the date of resection until death, and otherwise censored at the last follow-up. The survival distributions were estimated using Kaplan-Meier methods, and the difference in survival distributions between groups were compared using log-rank test. Multivariable Cox proportional hazard model was used to adjust baseline variables in evaluating the difference between two groups. For the multivariable model, all variables were included in the model, and backward variable selection with elimination criteria of 0.2 was used for variables other than group variable. Results were considered statistically significant when the probability values were <0.05. All statistical analyses were performed using SAS 9.2 and R (version 3.0, SAS Institute Inc., Cary, NC, USA) statistical software.

RESULTS

Patients and tumor characteristics

Table 1 summarizes the patients' characteristics. Among the 77 patients 49 were male. Mean age was 62.3 (range 38−79), 27 patients were with synchronous metastasis, while the rest were with metachronous metastasis. Forty four patients received postoperative systemic chemotherapy firstly, and

Table 1. Clinical and demographic characteristics

Characteristic	No. of patients (%)			*p* value
	Total (n=77)	Chemo first (n=44)	RT first (n=33)	
Sex				0.3384*
M	49	26 (59.1)	23 (69.7)	
F	28	18 (40.9)	10 (30.3)	
Age in yrs mean (range)	62.3 (38−79)	63.3 (46−79)	60.9 (38−76)	0.2305†
Tumor location				0.7184‡
Supratentorial	69	40 (90.9)	29 (87.9)	
Infratentorial	8	4 (9.1)	4 (12.1)	
Timing of metastasis				0.0848*
Synchronous	27	19 (43.2)	8 (24.2)	
Metachronous	50	25 (56.8)	25 (75.8)	
KPS score				0.5505*
≥70	63	35 (79.6)	28 (84.9)	
<70	14	9 (20.5)	5 (15.2)	
RPA class				0.0328‡
1: I (age<60, no systemic ds, KPS≥70)	8	1 (2.3)	7 (21.2)	
2: II (any one of those)	56	35 (79.6)	21 (63.6)	
3: III (KPS<70)	13	8 (18.2)	5 (15.2)	
Median follow-up time (range)	15.9 (3.5−85.1)	16.7 (3.5−85.1)	15.7 (5.0−80.3)	

*Pearson chi-square test, †t-test, ‡Fisher exact test. RT, radiotherapy; KPS, Karnofsky performance status; RPA, recursive partitioning analysis

among them 26 patients received whole brain radiation therapy after progression of brain disease. Adjuvant whole brain radiation therapy was carried out firstly in 33 patients, and among them 22 patients received chemotherapy after radiation therapy. No significant difference was observed between the two groups (adjuvant RT vs. chemotherapy) in terms of demographic parameters, disease type, tumor location, timing of metastasis, KPS score except RPA class. The median follow-up duration was 15.9 months (range 3.5−85.1 months).

Local and distant recurrence rate

Among the 77 patients, there were 19 (24.7%) local recurrences, among which 7 (21.2%) were in the adjuvant RT group and 12 (27.3%) were in the chemotherapy group (p= 0.542). As for distant recurrence, 7 (21.2%) distant recurrences occurred among 33 patients in the adjuvant RT group and 27 (62.4%) among 44 in the chemotherapy group (p<0.0005).

Survival

The log-rank test of patients' survival in terms of LRF, DRF, DFS, and OS showed no significant difference between the two groups with p-values=0.8993, 0.4489, 0.1522, and 0.8005, respectively (Fig. 1).

After adjusting other baseline covariates (Table 2), the dif-

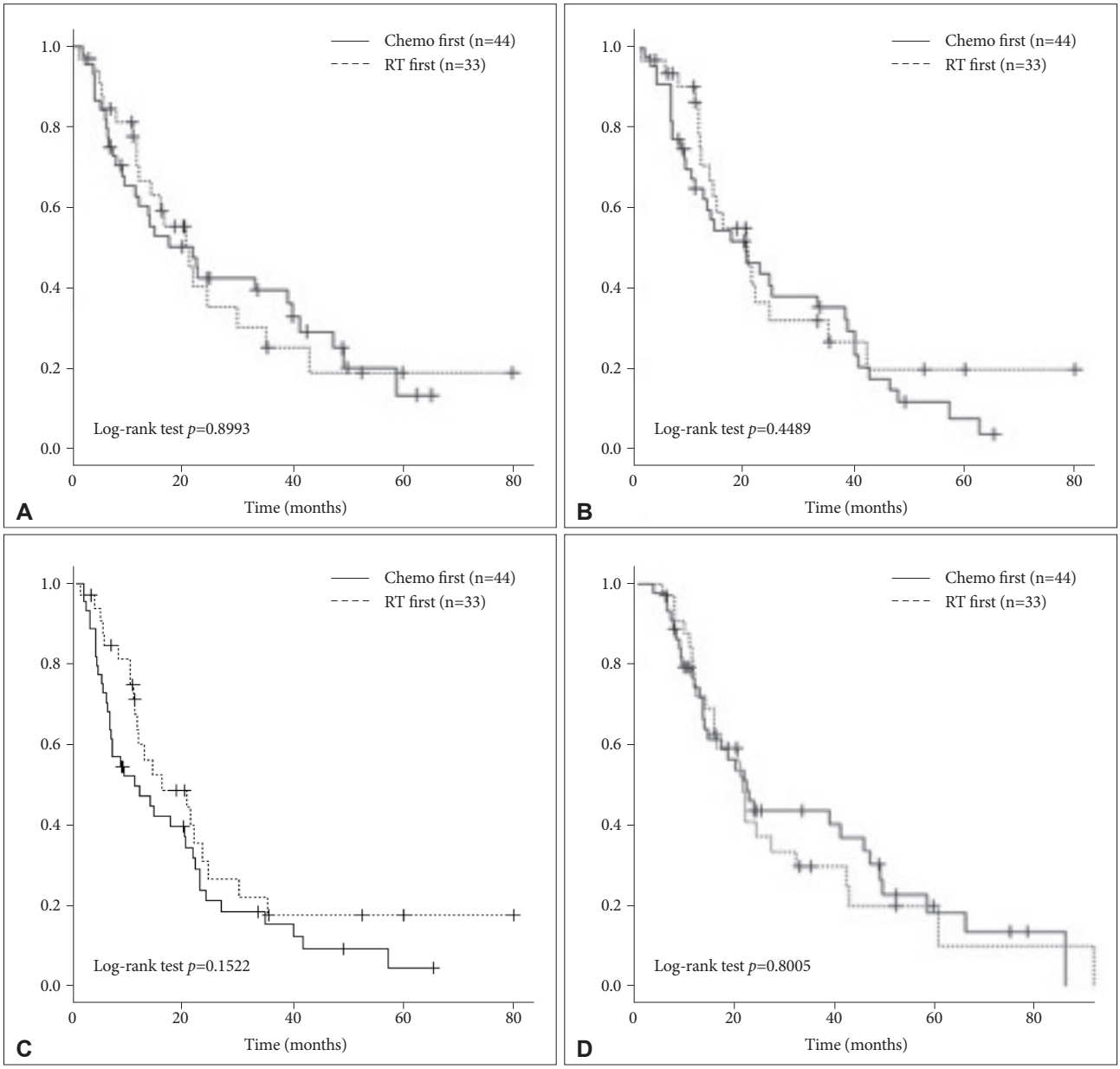

Fig. 1. Kaplan-Meier curves for all patients. A: Local recurrence or death. B: Distant recurrence or death. C: Local recurrence or distant recurrence or death. D: Overall survival. RT, radiotherapy.

Table 2. Univariable and multivariable analysis based on Cox proportional hazard model for local recurrence (LRF) and distant recurrence free survivals (DRF)

	LRF				DRF			
	Univariable HR (95% CI)	*p*-value	Multivariable HR (95% CI)	*p*-value	Univariable HR (95% CI)	*p*-value	Multivariable HR (95% CI)	*p*-value
	n=77	Event=51	n=77	Event=51	n=77	Event=55	n=77	Event=55
Group								
Chemo first	1		1		1		1	
RT first	0.96 (0.55–1.7)	0.8997	0.90 (0.48–1.71)	0.7488	0.81 (0.46–1.41)	0.4483	0.87 (0.46–1.65)	0.6782
Sex								
M	1		1		1			
F	0.53 (0.29–0.97)	0.0381	0.66 (0.35–1.24)	0.1968	0.55 (0.31–0.97)	0.0372		
Age	1.03 (1–1.07)	0.0499	1.04 (1.00–1.08)	0.0627	1.04 (1.01–1.08)	0.0171	1.04 (1–1.08)	0.0494
Tumor location								
Supratentorial	1		1		1		1	
Infratentorial	3 (1.23–7.32)	0.0157	5.03 (1.83–13.79)	0.0017	2.63 (1–6.94)	0.0502	4.18 (1.44–12.13)	0.0085
Timing of metastasis								
Synchronous	1				1			
Metachronous	0.93 (0.52–1.66)	0.8124			0.84 (0.49–1.45)	0.5331		
KPS score								
≥70	1				1			
<70	1.91 (0.97–3.74)	0.0601			2.01 (1.05–3.85)	0.0346		
RPA class								
I (age<60, no systemic ds, KPS≥70)	1	(0.0236)	1	(0.078)	1	(0.0135)	1	(0.0373)
II (any one of those)	2.23 (0.79–6.31)	0.132	1.48 (0.47–4.67)	0.5034	3.65 (1.12–11.89)	0.0314	2.32 (0.64–8.37)	0.1978
III (KPS<70)	4.52 (1.42–14.38)	0.0105	3.08 (0.91–10.38)	0.0698	6.61 (1.83–23.92)	0.004	4.76 (1.25–18.1)	0.0219

HR, hazard ratio; RT, radiotherapy; KPS, Karnofsky performance status; RPA, recursive partitioning analysis; CI, confidence interval

ference still remained to be not significant with adjusted *p*-values of 0.7448 and 0.6782, respectively for LRF and DRF.

DISCUSSION

Several treatment modalities have been reported to be effective as an adjuvant therapy after surgical resection of metastatic brain tumor from NSCLC. For solitary brain metastasis, surgery plus WBRT have been considered as a standard treatment modality that resulted in reduced brain disease recurrence [16-20]. However, it has been reported that WBRT does not improve OS and functional independence. WBRT may impair cognitive function due to leukoencephalopathy and brain atrophy, and as the survival of patients with brain metastasis become longer, there is increasing concern regarding quality of life and tendency to defer WBRT with close brain image follow ups. Our hypothesis is that chemotherapy after surgery for metastatic brain tumor enables concurrent treatment of systemic disease and remnant microscopic metastatic brain tumors, and that radiation therapy after brain disease progression may also be effective. Brem et al. [21] reported that carmustine wafer on the resection cavity after resection of a single brain metastasis resulted in reduced risk of a local recurrence without WBRT independent of the primary cancer site of origin. Also, the patients showed improved memory and other executive cognitive function [21]. The local control rate (78%) was comparable to reported rates after surgery with WBRT and superior to reports of WBRT alone [21]. These results showed that chemotherapy may be effective against microscopic remnant metastatic brain tumor cells if enough drug delivery can be achieved. However, there are no previous reports about the effect of postoperative adjuvant systemic chemotherapy in metastatic brain tumors. Previously, we suggested that brain metastases may be treated with frontline systemic chemotherapy alone, and frontline chemotherapy may be helpful for patients with metastatic brain tumors in terms of cognitive function and quality of life compared with WBRT [4]. Systemic treatment for patients with NSCLC including chemotherapy and molecular-targeted therapy improved dramatically recently, such progress initiate us to evaluate the role of systemic treatment as a postoperative adjuvant setting for brain metastasis from NSCLC.

In this retrospective analysis, we demonstrated that there was no significant difference in terms of patients' survival between patients who received postoperative systemic chemotherapy and those who received adjuvant brain RT. Distant recurrence occurred more frequently in the chemotherapy group. However, the DRF survival was not different between the two groups. This is probably because the causes of death were mostly primary cancer progression rather than brain metastasis progression. In our cases series, 70% of patients died of primary cancer progression, and we had also reported previously the growth rate of metastatic brain tumor from NSCLC. The volume doubling time was about 3 months [22,23]. After resection of metastatic brain tumors, we usually followed up patients with brain MRI or CT every 3 months, and since most of the local or distant brain metastases appeared as small asymptomatic lesions, administration of radiation therapy after brain disease progression is discovered may also be effective. Postoperative chemotherapy is more feasible and may be an appropriate option for simultaneous control of both primary and metastatic lesions. Among the adjuvant RT group, 67% of all patients received chemotherapy after RT. Among the chemotherapy group, 59% of all patients received RT for brain lesion progression. As a result, 41% of all patients did not receive RT until death or last follow-up. Therefore, this suggests that we may avoid unnecessary radiation therapy in almost 40% of patients with this strategy.

In conclusion, there is no significant difference in terms of patients' survival between patients who received postoperative systemic chemotherapy and those who received adjuvant brain RT. Although these findings are thought provoking, these must be interpreted cautiously because of the nature of the retrospective analysis and relatively small number of cases in the present study. For further evaluation, prospective randomized phase III clinical trials for larger number of patients are surely needed.

Conflicts of Interest

The authors have no financial conflicts of interest.

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