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Findings and Outcomes from a Retrospective Study of Non-Small Cell Lung Cancer Patients with Synchronous Solitary Brain Metastases. An Analysis of Six Cases

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Abstract: *Background*: The combined resection of primary non-small cell lung cancer (NSCLC) with synchronous solitary brain metastasis (SSBM) after treatment of SSBM is superior to other treatments for prolonging patients survival. This study reviewed the clinical records and follow-up data of six patients with NSCLC and SSBM to verify the validity of this treatment.

Methods: Six NSCLC patients presenting with SSBM, who were treated at Hamamatsu University School of Medicine Hospital between January 2000 and December 2010, were retrospectively reviewed.

Results: There was one long-term survival case. The mean follow-up time was 37 months. The 1- and 5-year overall survival rates for all patients were 50% and 33%, respectively. The median survival time (MST) for all patients was 40 weeks.

Conclusion: Primary tumor resection in a NSCLC patients with SSBM is therefore considered to be an acceptable and effective surgical approach.

Keywords: Aggressive trimodality treatment, Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI), Five-year tumor-free survival, Gamma knife stereotactic radiosurgery, Non small-cell lung cancer, Synchronous solitary brain metastasis.

INTRODUCTION

Lung cancer is the leading cause of cancer death in both males and females in Japan. Approximately, 20% of all patients with lung cancer develop brain metastasis [1]. Almost all patients with brain metastasis have been treated with whole-brain radiotherapy (WBRT), with-WBRT induced tumor shrinkage correlates with better survival and neurocognitive function [2]. However, this treatment modality often results in neurological toxicity [3]. A recent study showed that gamma knife surgery (GKS) for non-small cell lung cancer (NSCLC) with brain metastasis affords effective local tumor control in approximately 84% of patients [4]. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommends initially treating the brain lesions with NSCLC, followed by further treatment options for these patients with T1-2, N0-1 or for those with T3N0 including 1) surgical resection of the lung lesion followed by chemotherapy (category 2B); 2) Stereotactic radiosurgery (category 2B); or 3) additional chemotherapy followed by surgical resection of the lung lesion (category 2B) [5].

A growing body of literature suggests that selected patients with solitary brain metastasis from NSCLC can achieve long-term survival following metastatectomy if the primary lung cancer is also resectable. Several previous studies have demonstrated 5-year survival rates ranging between 15 and 35% after a resection of solitary brain metastasis [6-9]. A retrospective study was conducted to verify validity of the current treatment protocol.

METHODOLOGY; PATIENTS

The database of this institution was searched to identify any patients that had undergone surgical resection between January 2000 and December 2010. Six patients presenting with synchronous solitary brain metastasis (SSBM) underwent surgical resection of primary NSCLC. The medical records of each patient were examined for age, sex, histological type, preoperative clinical stage of the primary tumor, postoperative pathological stage of the primary tumor, surgical procedure, and preoperative chemotherapy. The characteristics of the patients are listed in Table **1**. The median age was 60 years with a range of 51 to 78 years. One patient had neurological symptoms, seizure and hemiplegia. Three patients had pulmonary symptoms, including bloody phlegm and an enlargement of the cervical lymph node. One patient had a cough plus chest pain. The preoperative workup included chest computed tomography (CT), brain magnetic resonance imaging (MRI) or brain CT, and bone scans.

Patients with synchronous primary lung cancer and SSBM were treated by pulmonary resection and neurosurgical intervention after preoperative systemic

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Table 1. Characteristics of NSCLC Patients with Synchronous Brain Metastases (n=6)

Case	Age (y)	Sex	Histology	Clinical Stage	Pathological Stage
1	64	F	Adenosquamous	T1a N0	T2a N2
2	78	F	Adeno	T3 N1	T2 N2
3	54	F	Adeno	T3 N0	T3 N0
4	51	M	Adeno	T2b N0	T2b N0
5	55	M	Adeno	T1bN3	T4 N3
6	72	M	Adeno	T2a N0	T4 NX

chemotherapy. The basic surgical procedure was lobectomy, which is standard; however, pulmonary resection included lobectomy in four patients, while also including one wedge resection and one exploratory thoracotomy (Table **2**). A wedge resection was performed for diagnosis. Exploratory thoracotomy was performed because of pleural dissemination. No patient had preoperative mediastinoscopy or endobronchial ultrasonography (EBUS).

Follow-up was carried out *via* outpatient visits. Patients with any other anatomically distant metastasis (e.g. liver, bone, adrenal) were not included in this study. The clinical and pathological stages were distributed according to 7th edition of the Union for International Cancer Control (UICC) TNM classification [10]. Survival curves were plotted using the Kaplan-Meier method and compared by log-rank test. All statistical analyses were performed with the PASW statistics software package version 18 (SPSS, Inc., Chicago, IL).

RESULTS

This report presents the findings on the results of treatment of six patients containing one relapse-free, long-term survival case that was reported previously [11]. The patient had SSBM from NSCLC and survived without recurrence for five years following surgery after chemotherapy, even though the primary tumor was T3N0 thoracic stage IIB (Figs. **1A**, **2**). He first received four cycles of chemotherapy with carboplatin (AUC: 6; Paraplatin, Bristol-Myers Squibb, New York, USA) and paclitaxel (200mg/m$^{2;}$ Taxol, Bristol-Myers Squibb) every three weeks, and received concurrent GKS for the treatment of SSBM. The brain metastasis was well controlled after four cycles of chemotherapy, and the primary tumor showed an 18% reduction in size. He underwent right upper lobectomy and an *en bloc* chest wall resection of three ribs with hilar and mediastinal lymph node dissection because he had no evidence of new metastasis. The histopathological examination revealed poorly differentiated adenocarcinoma with invasion to the subpleural soft tissue; pT3N0M1b, stage IV. He was next administered oral tegafur-uracil (250mg/m^2; UFT, Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) because refused postoperative adjuvant platinum-based chemotherapy. The brain metastasis disappeared completely (Fig. **1B**), and he has survived for five years since the surgery without recurrence.

Complete pulmonary resection and lymph node dissection were performed in four patients. Five patients had adenocarcinoma, and one had adenosquamous carcinoma. In the preoperative diagnosis, lymph node metastases were identified in two patients, including one N1 patient and one N3 patient. However, more lymph node metastases were detected by a pathological examination. Specifically, pathological lymph node metastases were identified in three patients, including N2 in two patients, and N3 in one.

One patient received chemoradiotherapy, consisting of a combination of cisplatin (Randa, Nippon Kayaku Co., Ltd, Tokyo, Japan) and vinorelbine (Navelbine, Kyowa Hakko Kirin Co., Ltd, Tokyo, Japan) and concurrent thoracic radiotherapy at a dose of 45Gy. She then received additional chemotherapy with carboplatin and paclitaxel. Four patients received chemotherapy alone, the regimens consisting of a combination of carboplatin and paclitaxel in two patients, gemcitabine (Gemzar, Eli Lilly Japan K.K., Kobe, Japan) and vinorelbine, and cisplatin and docetaxel (Taxotere, sanofi-aventis K.K., Tokyo, Japan) and fluorouracil (5-FU,

Table 2.

Case	Preoperative Treatment (Cycle)	Surgical Procedure	Postoperative Treatment	Recurrence	Outcome
1	CBDCA + PTX (1)	Lobectomy	Chemotherapy	Pleural dissemination	Died 9months
2	None	Lobectomy	None	None	Died 57 days (TRD: ARDS)
3	CDDP + VNB (2) + radiation, CBDCA + PTX (2)	Lobectomy	Radiation	Bone, lung	Died 9months
4	CBDCA + PTX (4)	Lobectomy	UFT (adjuvant)	None	Alive 79 months
5	CDDP + DOC + 5-FU (2)	Wedge resection	Gefitinib	Bone, LN	Died 99 months
6	GEM + VNB (1)	Probe thoracotomy	Gefitinib	Brain, bone	Died 24months (TRD: IP)

Abbreviations: CBDCA: carboplatin; PTX: paclitaxel; GEM: gemcitabin; VNB: vinorelbin; CDDP: cisplatin; DOC: docetaxel; 5-FU: 5-fluorouracil; TRM: treatment-related death; ARDS: acute respiratory distress syndrome; IP: interstitial pneumonia; LN: lymph node
(1): the date of the last follow-up from the primary operation.

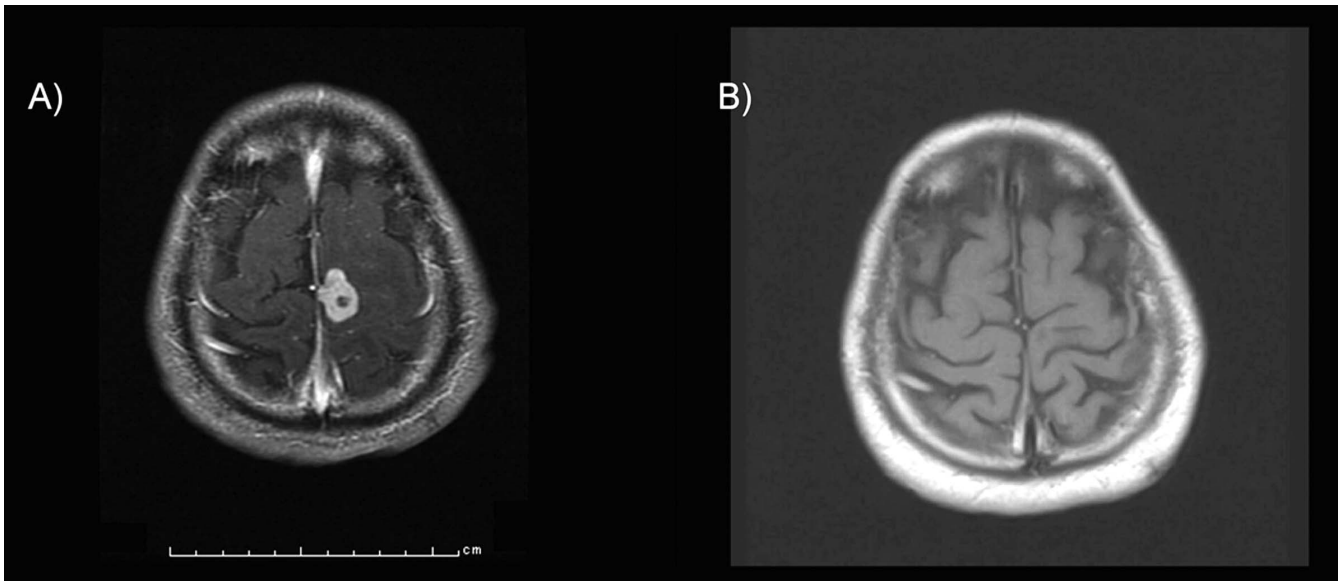

Fig. (1). A) Contrast-enhanced MRI of the brain at the time of GKS showing a 20×16mm nodule in the left frontal lobe. **B**) Follow-up findings of a patient with local control at 5 years. Brain metastasis had disappeared.

Kyowa Hakko Kirin Co., Ltd) in one each. The mean follow-up time was 37 months.

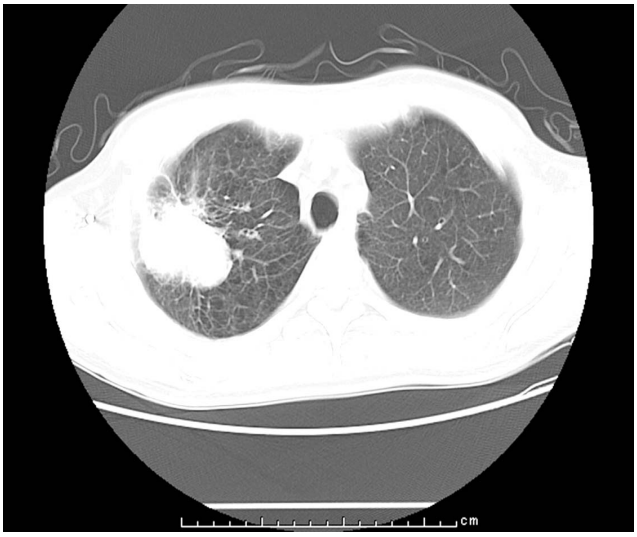

Fig. (2). Chest CT scan showing a 60 mm mass in the right upper pulmonary lobe. The tumor invaded the chest wall.

The 3- and 5-year survival rates for all patients were 50% and 33%, respectively (Fig. **3**). The median survival time (MST) for all patients was 40 weeks. There was one relapse-free long-term survival case of 79 months. Five patients died; three were cancer deaths and two were treatment-related deaths (TRD). Of note, there was one long-term tumor-bearing survivor of 99 months. However, the patient cannot expect a long-term survival because the primary tumor was T4N3 advanced cancer. Nevertheless, he was able to survive a long time due to being treated with Gefitinib (Iressa, AstraZeneca K.K., Osaka, Japan) after the recurrence of lung cancer. Two cases of TRD were multi organ failure caused by acute respiratory distress syndrome 57 days after surgery and interstitial pneumonia associated with Gefitinib.

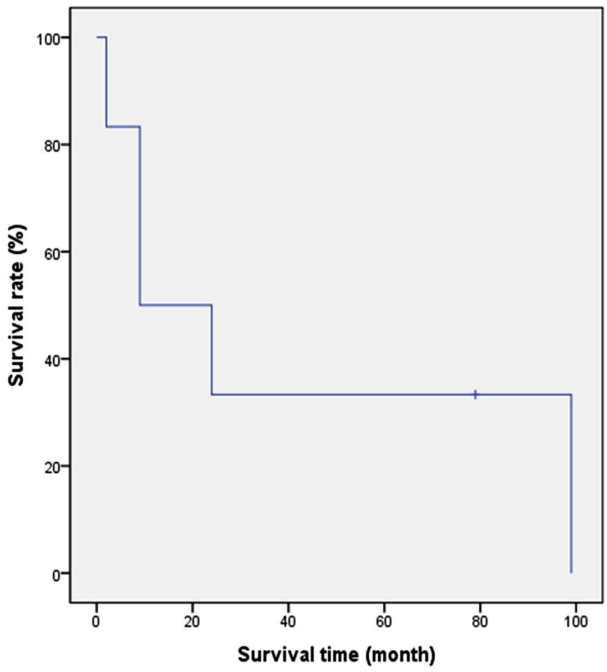

Fig. (3). Kaplan-Meier overall survival curve from the time of the pulmonary resection for the 6 patients.

DISCUSSION

The diagnosis of synchronous lung cancer and a SSBM usually rules out surgical resection as a therapeutic option. However, some of these patients have a chance of better local control and an improved survival rate. Several reports on brain metastases have been published [6-9, 12-14]. General advances in neurosurgical microscopic techniques, radiotherapy and chemotherapy have allowed better local control of intracranial metastasis from NSCLC, resulting in a longer life expectancy and better quality of life. Several studies showed the validity of the GKS, thus demonstrating

not only a survival benefit and lower neurological death rates, but also a shorter hospital stay and reduced frequency of toxicity [4, 15, 16].

Mean overall-survival has been reported to range from 12 to 52 months (Table **3**). Torre *et al*. [7] published a report on a series of 27 patients, including 21 that underwent synchronous surgery, with an overall 5-year survival rate of 15%, and a mean survival of 26 months. A more positive outcome was obtained in both the patients without node metastases at the time they underwent thoracotomy and in the patients with supratentorial metastases. Burt *et al*. [13] analyzed 65 patients with SSBM diagnosed within 60 days after the primary NSCLC. The 32 patients who underwent complete lung resections had survival rates of 71%, 16%, and 16% at 1, 5, and 10 years, respectively (MST: 21 months), in comparison to the survival rates of 40%, 4%, and 0% at 1, 5, and 10 years respectively, for patients who did not have complete resections (MST: 10 months). A multivariate analysis demonstrated that locoregional stage had no significant effect on survival time (p=0.97) but that complete resection of the primary disease significantly prolonged survival time (p=0.002). Mussi *et al*. [12] reported on 45 patients who underwent bifocal resections for a primary lung tumor and brain metastasis. The 5-year survival rate for the 15 patients with synchronous presentation was 6.6% with a median survival of 18 months; 14 of those patients died within 30 months, with one patient surviving for 63 months. The only variable that was significantly associated with a longer survival time was a squamous lung cancer histology (p=0.02). Iwasaki *et al*. [14] reported on a series of 70 patients with brain metastasis from NSCLC, 41 of them undergoing bifocal resections. The 1- and 3-year survival rates after treatment of the brain were 66.4 and 22.9% with an MST of 954 days following primary surgery. Bifocal resections afford patients an extended survival time in comparison to the survival of the lung only resection group. A multivariate analysis demonstrated that adenocarcinoma histological subtype (p=0.0035), node status (p=0.0366) and high serum carcinoembryonic antigen (CEA; p=0.0103) are independent prognostic factors. The current study also indicates that accurately determining mediastinal lymph node status is an important clinical problem. Undetected mediastinal metastases are a major cause of unnecessary thoracotomy, occurring in 28% of patients [19]. Imaging with CT and fluorodeoxyglucose positron emission tomography (PET) is neither sensitive nor specific enough to detect the presence or absence of node metastasis, and therefore mediastinal tissue staging is frequently indicated in patients with nonmetastatic resectable lung cancer [17, 18]. Mediastinoscopy is one of the primary modalities in the evaluation of mediastinal lymph nodes, and recently some studies showed the validity of EBUS [20, 21]. Annema *et al*. [21] showed that the sensitivity and negative predictive value for surgical staging by mediastinoscopy *vs* endosonography alone was 79% (95% CI, 66-88%) *vs* 85% (95% CI,74-92%; p=0.47) and 86% (95% CI, 76-92%) *vs* 85% (95% CI, 75-92%) respectively (p>0.99). A combination of these modalities improves the precision, and extends the survival time avoiding unnecessary thoracotomy.

The NCCN guideline showed that the 5-year survival rate with SSBM ranges from 10% to 20%, with the median survival time being about 40 weeks. The MST of 40 weeks in the current study is therefore the same. Although mostly patients with advanced primary tumors were included in the current study, the MST was equivalent to the NCCN guidelines. In general, our patient cannot expect a long-term survival because the primary tumor was T4N3 advanced cancer. Nevertheless, the patient was able to survive a long time, namely 99 months. This is because the patient was treated with Gefitinib after the recurrence of lung cancer. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) made it possible for tumor-bearing patients to survive long term. However, a radical cure is not obtained in Gefitinib. If a complete resection is possible, then aggressive trimodality therapy of the primary site and brain metastasis may be an effective treatment for locally advanced NSCLC patients with SSBM for a radical cure.

In conclusion, since the current study is a retrospective investigation covering a period of over 10 years, the chemotherapy doses and regimens were therefore diverse within the group of cases. Although the patient number was small in this study, we did identify one five-year, disease-free survival patient and one long-term tumor-bearing survivor of 99 months, indicating that the surgical treatment of lung cancer with brain stage IV metastases is beneficial when indicated. It is now evident that as this was a

Table 3. Surgical Results of Combined Management for Synchronous Solitary Brain Metastasis and Primary Lung Cancer

Author	Year	No.	Therapy for Brain Metastasis	5-Year Survival (%)	Median Survival (Month)	Poor Prognostic Factors
Torre *et al.* [5]	1988	27	Craniotomy	15	26	Lymph node metastasis
Burt *et al.* [12]	1992	65	Craniotomy	16	21	Incomplete resection
Mussi *et al.* [11]	1996	45	Craniotomy	6.6	18	Non-squamous cell carcinoma
Billing *et al*. [6]	2001	28	Craniotomy	21	24	Lymph node metastasis
Bonnette *et al.* [7]	2001	103	Craniotomy	11	12.4	Non-adenocarcinoma
Iwasaki *et al.* [13]	2004	70	Craniotomy	22.9*	954**	Adenocarcinoma, lymph node metastasis and high serum CEA
Lo CK *et al*. [4]	2010	17	Craniotomy and SRS	27	52	-
Current study	2012	6	SRS	33	40	-

*: 3-year survival, **: Median survival (day).

retrospective study, and a prospective study to evaluate the survival benefit of aggressive treatment for both primary site cancer and brain metastases in patients demonstrating locally advanced NSCLC with SSBM will thus be necessary.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Declared none.

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