Original Article

Long-term survival without surgery in NSCLC patients with synchronous brain oligometastasis: systemic chemotherapy revisited

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Background: Among patients with metastatic non-small-cell lung cancer (NSCLC), patients with TNM stage N0 to N1 and brain oligometastases (BOM) (less than 5 metastases) as the sole distant lesion (N0–1 BOM) who receive surgical treatments for the primary and metastatic sites reportedly have a better prognosis. Little data is available regarding the outcomes of patients treated with only systemic chemotherapy for the primary site and definitive treatment for synchronous BOM, compared with the outcomes of patients receiving surgical treatment for the primary site.

Methods: Stage IV NSCLC patients with or without N0–1 BOM, who underwent chemotherapy for the primary site between January 2000 and December 2010 were identified from the records of our institution.

Results: Among 936 advanced NSCLC patients treated with systemic chemotherapy, 19 patients had N0–1 BOM at presentation. The median overall survival (OS) period of the N0–1 BOM patients was 16.0 months (95% CI, 11.8–20.2 months), while that of the N2–3 BOM + non-BOM patients was 14.5 months (95% CI, 13.2–15.8 months), compared with 7–9 months in previous reports. The median 3- and 5-year survival rates of the N0–1 BOM patients were 28% and 19%.

Conclusions: The treatment outcomes of the N0–1 BOM patients who did not receive surgery for the primary site were better than those of the N2–3 BOM + non-BOM patients. A randomized trial evaluating the efficacy of surgery for the primary site in N0–1 BOM patients is warranted.

Keywords: Lung cancer; oligometastases; brain metastases; chemotherapy, incidence

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Introduction

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. Among patients with NSCLC, 30–50% of patients have distant metastases and 7.4–10.0% have brain metastases at the time of diagnosis (1,2). Advanced stage NSCLC patients have a poor prognosis. The 5-year survival rate for these patients has been reported to be less than 10% (3). Among patients with metastatic NSCLC, brain metastases are correlated with a shorter survival time (4).

Hellman *et al.* proposed a clinically significant status known as oligometastasis, which was initially described as a restricted locoregional status (5). Oligometastasis is now defined as a small number of isolated distant metastases

(generally less than 5 sites) (6). An incidence rate of 4.0% has been reported for brain oligometastasis (BOM) as the sole distant lesion in patients with NSCLC (any N grade) receiving surgical treatment (7). A few studies have reported patients with TNM stage N0 to N1 BOM (N0–1 BOM) who did not receive surgical treatment.

The standard treatment for stage IV NSCLC is chemotherapy. A few studies have reported that patients with BOM who receive surgical treatments for both their primary and metastatic sites have a better prognosis (8-15). However, a comparison of the survival outcomes for NSCLC patients with BOM undergoing either surgery or chemotherapy for the primary site has not yet been performed.

The purpose of this retrospective study was to investigate the frequency and treatment outcome of patients with N0–1 BOM who received chemotherapy as a treatment for the primary site and definitive treatment for brain metastases.

Methods

Patients with stage IV lung cancer who received chemotherapy at the National Cancer Center Hospital in Japan between 2000 and 2010 were included in this analysis. We selected NSCLC patients with brain involvement (less than 5 metastases) as the sole distant lesion at the time of diagnosis (synchronous metastases) (6,16). Among those patients, N0–1 stage NSCLC cases who were a candidate for resection surgery of the primary lesion if they did not have brain metastases were included in this study. All the patients were evaluated using computed tomography (CT) examinations of the chest and abdomen, magnetic resonance imaging (MRI) and/or CT of the brain, and a bone scan and/or PET-CT if available as a standard staging work-up to investigate distant metastases before receiving chemotherapy. Patients were staged using the 7th edition of the Union for International Cancer Control TNM classification for lung cancer. Patient age, sex, performance status (PS), histology, information on driver oncogenes [*EGFR*, and anaplastic lymphoma kinase (*ALK*) rearrangement], TNM staging, number of brain metastases, maximum size of brain metastases, initial systemic treatment (chemotherapy or molecular targeted therapy), initial treatment for the brain metastases (surgery, whole brain irradiation, stereotactic radiotherapy), pattern of recurrence after initial treatment, and second-line systemic therapy regimens were collected. This study was approved by the institutional review board of the National Cancer Center Hospital [2014-160].

Statistical analysis

OS was defined as the interval between the date of initial treatment (systemic chemotherapy or local therapy for brain metastases) and the date of death or the most recent date of follow-up for surviving patients. PFS was measured from the date of initial treatment until death before progression, the date of disease progression, or the most recent date of follow-up for surviving patients without progression. PFS and OS were estimated using the Kaplan-Meier method. SPSS version 19 (SPSS, Chicago, IL, USA) was used for the statistical analyses.

Results

Patient characteristics

A total of 1,306 patients with stage IV NSCLC who were treated at our hospital were identified. The cohort diagram is shown in *Figure 1*. We excluded 370 patients: 123 patients who did not receive any treatment for the primary site, and 247 patients who did not have histological confirmation of NSCLC. We identified 19 patients (2.0%) with brain involvement (less than 5 metastases) as the sole distant lesion and N0 or N1 disease as N0–1 BOM patients and 917 stage IV NSCLC patients who received chemotherapy with or without radiation for treatment of the primary site as N2–3 BOM + non-BOM (no brain metastasis or more than 5 brain metastases) patients. The median duration of the follow-up period for the 19 N0–1 BOM patients was 16.0 months (range, 3.0 to 88.7 months). Four of the 19 patients were lost to follow-up but were not reported to have died, and one patient was still alive at the time of the study cut off (October 2016). The patient characteristics are summarized in *Table 1*. Among the N0–1 BOM patients, the histological findings showed 17 adenocarcinomas (90%), 1 squamous cell carcinoma (5%), and 1 large cell carcinoma (5%). One patient (5%) had an activated mutation (L858R) of the epidermal growth factor receptor (*EGFR*) gene, 3 patients (16%) had wild-type *EGFR*, and 15 patients (79%) had an unknown *EGFR* status. None of the patients had an *ALK* oncogene rearrangement, 1 patient (5%) had a negative result, and 18 patients (95%) were not examined. The brain metastases consisted of 1 site in 10 patients (53%), 2 sites in 7 patients (37%), 3 sites in 1 patient (5%), and 4 sites in 1 patient (5%). In 7 cases (37%), the maximum

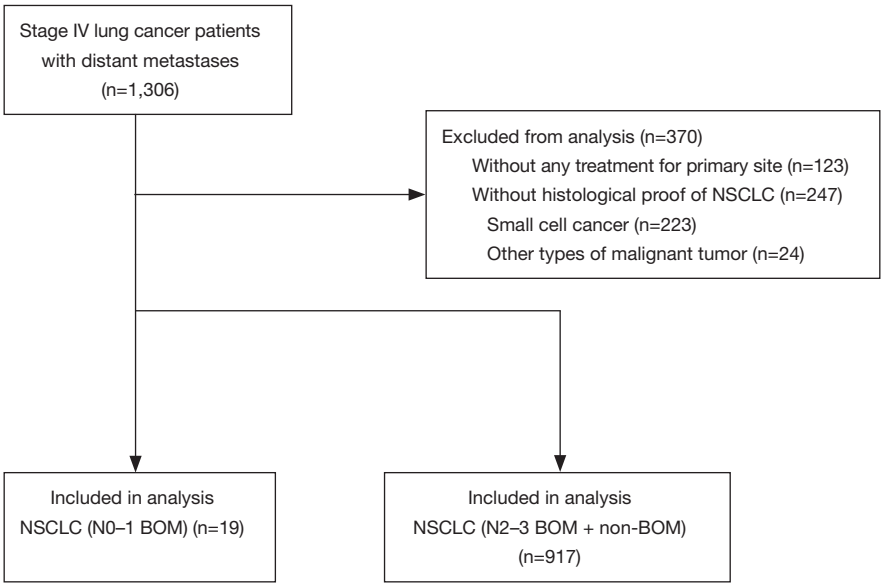

Figure 1 Consort diagram.

diameters of the brain metastases were more than 30 mm. Three patients (16%) received brain surgery, 5 patients (26%) received whole brain radiation therapy (WBRT), 5 patients (26%) received stereotactic radio surgery (SRS), and 6 patients (32%) received only systemic chemotherapy for the initial management of the brain metastases. The primary systemic therapies were cytotoxic chemotherapy in 17 patients (90%) and *EGFR* tyrosine kinase inhibitor (*EGFR*-TKI) in 2 patients (11%). All the first-line systemic cytotoxic chemotherapy regimens were platinum-based regimens.

Efficacy of chemotherapy and survival benefit

The median PFS of the N0–1 BOM patients was 5.5 months (95% CI, 4.3–6.7 months), while that of the N2–3 BOM + non-BOM patients was 4.7 months (95% CI, 4.3–5.1 months). The Kaplan-Meier curve for PFS is shown in *Figure 2*. Among the N0–1 BOM patients, 5 patients had local recurrences, 13 patients had distant metastases or mixed recurrences (3 with brain and thoracic sites, 1 with brain and distant sites, 1 with thoracic and distant sites, and 8 with distant metastasis). Among the 9 patients who developed brain recurrences, 6 patients had received brain radiotherapy (3 had received WBRT, and 3 had received SRS) and the other 3 patients had not received brain radiotherapy. Four patients (21%) had received *EGFR*-TKI and 8 patients (42%) had received cytotoxic agents. The median 3- and 5-year survival rates of the N0–1 BOM patients were 28% and 19%, respectively. The median OS of the N0–1 BOM patients was 16.0 months (95% CI, 11.8–20.2 months), while that of the N2–3 BOM + non-BOM patients was 14.5 months (95% CI, 13.2–15.8 months). There were no statistically difference between two arms in the OS (P=0.13) and PFS (P=0.782) using log rank test. The Kaplan-Meier curve for OS is shown in *Figure 3*. There were 2 long-term survivors with N0–1 BOM who survived for more than 5 years. One patient was followed without treatment for more than 5 years after one cycle of platinum-containing chemotherapy and palliative local radiation therapy. This patient died of disease progression. Another patient was observed without treatment for more than 2 years after receiving 6 lines of chemotherapy and radiation therapy for the brain metastases. Despite not having any of the common *EGFR* mutations, this patient received *EGFR*-TKI and survived without disease progression for 2 years.

Discussion

The frequency of N0–1 BOM was 2.0% among patients with stage IV NSCLC. The 3- and 5-year survival rates in patients with N0–1 BOM were 28% and 19%, respectively. This is the first report describing the treatment outcome of chemotherapy without surgical resection and radiotherapy for the primary site in NSCLC patients with brain involvement as a single-organ metastasis.

Few reports have described the incidence of

Table 1 Patient characteristics

Characteristics	N0–1 BOM (n)	N2–3 BOM + non-BOM (n)
Sex		
Male	13	570
Female	6	347
PS		
0	6	290
1	13	551
2–4	0	76
Histological type		
Adenocarcinoma	17	716
Squamous	1	95
Large cell	1	24
Others	0	82
T stage		
1	7	96
2	7	206
3	4	51
4	1	564
N stage		
0	12	126
1	7	65
2–3	0	726
Number of brain metastases		
1	10	NA
2	7	NA
3	1	NA
4	1	NA
Size of brain metastases		
≥3 cm	7	NA
<3 cm	12	NA
EGFR mutations		
Positive	0	NA
Negative	2	NA
Unknown	17	NA
ALK rearrangement		
Positive	0	NA
Negative	1	NA
Unknown	18	NA

ALK, anaplastic lymphoma kinase; BOM, brain oligometastases; EGFR, epidermal growth factor receptor; NA, not available; PS, European Cooperative Oncology Group Performance Status.

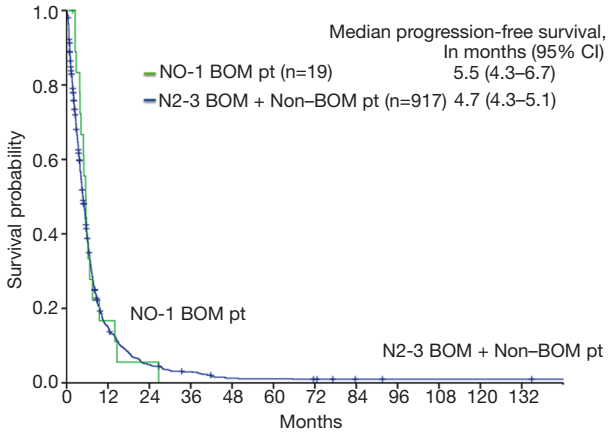

Figure 2 Kaplan-Meier curve for progression-free survival.

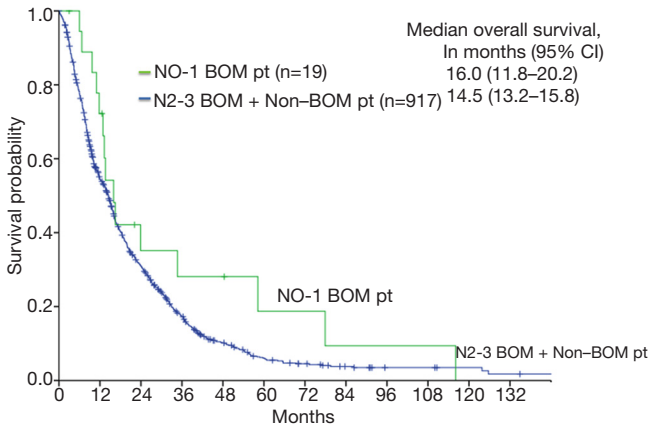

Figure 3 Kaplan-Meier curve for overall survival.

oligometastasis and BOM among NSCLC patients without surgery for the primary site. Brain metastases were reportedly detected in 7.4–10% of patients with NSCLC at presentation and in 30–50% of patients during therapy (2,17). In a previous report, 5.5% of NSCLC patients had oligometastases (1). Among the NSCLC patients referred to surgical departments, 4.0% of NSCLC patients had BOM (7). We reported that the frequency of patients with N0–1 BOM was 1.8% among those patients who were treated without surgical resection. According to previous studies, the incidence of BOM might range from 1.8% to 5.5%.

Advanced NSCLC patients usually have a poor prognosis and rarely survive for as long as 5 years. The median survival period for advanced NSCLC patients with brain metastases was 7-9 months according to previous studies (4,18-20). Radiation therapy or surgical treatment for brain

metastases improved the survival periods of these patients (21,22). The results of several randomized controlled trials have suggested three standard treatments for NSCLC patients with brain metastases: resection with sequential stereotactic radiation or whole brain irradiation, stereotactic radiation therapy alone, and stereotactic radiation therapy with sequential whole brain irradiation (18-20). Several reports have proposed that surgical treatment for the primary site improves the survival outcome, compared with chemotherapy +/– radiotherapy, but few reports have described the outcomes of cases treated with only chemotherapy +/– radiotherapy for the primary site. The leading cause of death among patients who have received local treatments for brain metastasis is the progression of primary and other metastatic lesions (23). There have been numerous published reports describing the combined resection of a primary lung site and a solitary brain metastasis (9,24,25). Surgical resection for both the brain and primary sites was suggested to prolong survival among NSCLC patients with a sole brain metastasis as early as 1976 (6,26). A recurrence-free rate of 6.3–14.0% at 4 years, a survival rate of 6.6–21.0% at 5 years, and a median survival time of 8.5–24.0 months were observed in trials including patients who underwent the resection of both the primary lesion and brain metastases (8,10,12,27). In trials using chemoradiotherapy for the treatment of the primary lesion and radiotherapy +/– resection for the brain metastases, the 2-year recurrence-free rate, the 5-year overall survival (OS) rate, and the median survival time were 53.0%, 7.6% and 13.1–31.8%, respectively (24,28,29). In the present study, the 5-year survival rate was 19% and the median survival was 16.0 months among the N0–1 BOM patients treated with chemotherapy for the primary site without surgical resection. This result suggests that the prognosis of patients without surgery was not worse than that of patients who received surgery for the primary site.

Patients with N0–1 BOM have a better prognosis, although the development of chemotherapy in recent years has contributed to an improvement in the survival outcome. The median OS of stage IV NSCLC patients with N0–1 BOM was 16 months, and this outcome was better than the OS of 6–9 months reported in previous trials among NSCLC patients who had brain involvement with or without other organ metastasis. According to the results of phase 3 trials among patients with advanced-stage unresectable NSCLC who received platinum-containing regimens (CDDP + PEM/CDDP + GEM/CBDCA + PTX), the median survival period was 10–18 months after initial chemotherapy (30-32). Although the survival time in our study was estimated after the treatment for the primary site or brain metastasis had begun, these results show that patients with N0–1 BOM have a relatively favorable prognosis (4,18-20). The survival outcome is expected to be further improved because of recent improvements in chemotherapies. Since one long-term survivor in this study received gefitinib for more than 2 years, the development of molecular target drugs is likely to improve the outcomes of NSCLC patients with N0–1 BOM.

Compared with previous reports, our results suggest that the treatment outcome of the N0–1 BOM patients without surgery for the primary site might be better than that of usual stage IV NSCLC patients and similar to that of those with chemoradiotherapy or surgery for the primary site. The guidelines established by the NCCN, ACCP, and ESMO include surgery for the primary lesion as a treatment option for patients with oligometastatic NSCLC and an N0–1 status. Several clinical trials evaluating the efficacy of chemoradiation therapy for NSCLC patients with oligometastases of distant lesions have been conducted (May, 2017). Further discussion of the role of surgery is needed based on balanced evidence comparing chemotherapy and surgical resection in oligometastatic NSCLC.

This report describes a relatively small retrospective study. Therefore, a selection bias might exist. Most of the patients in this study had been treated before the development of *EGFR*-TKIs, and the presence of *EGFR* mutations was not examined in these patients. In the present study, however, the impact of this circumstance on survival might be relatively small, since the number of patients treated with *EGFR*-TKIs after testing for *EGFR* mutations was also small. In oligometastatic brain metastases arm, three patients lost to follow up. The impact of these patients of survival analysis was small because all of them were considered that they were not capable of receiving additional chemotherapy, including *EGFR*-TKIs, for poor general condition. To further consider the development of molecular targeted drugs and immune-based therapy, further evaluation of driver mutations and the expression of programmed cell death-ligand 1 (PD-L1) is needed to select patients for future clinical trials. Addition to that, multi-institution study should be conducted, considering that it needs to find 19 patients for 10 years in single institution.

Conclusions

The frequency of N0–1 BOM patients with NSCLC who

received chemotherapy for their primary sites was 2.0% (19 out of 936). The PFS among the NSCLC patients with N0–1 BOM who received chemotherapy without resection surgery for the primary site was similar to that of patients who received resection surgery. A randomized trial comparing the efficacy of chemotherapy for the primary site with or without surgery is warranted.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the institutional review board of the National Cancer Center Hospital [2014-160]. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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