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Clinical Research

Long-term Surgical Outcomes in Oligometastatic Non-small Cell Lung Cancer: A Single-Center Study

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Background: We reviewed the clinical outcomes of patients with oligometastatic (OM) non-small cell lung cancer (NSCLC) who received multimodal therapy including lung surgery.
Methods: We retrospectively analyzed 117 patients with OM NSCLC who underwent complete resection of the primary tumor from 2014 to 2017.
Results: The median follow-up duration was 2.91 years (95% confidence interval, 1.48–5.84 years). The patients included 73 men (62.4%), and 76 patients (64.9%) were under the age of 65 years. Based on histology, 97 adenocarcinomas and 14 squamous cell carcinomas were included. Biomarker analysis revealed that 53 patients tested positive for epidermal growth factor receptor, anaplastic lymphoma kinase, or *ROS1* mutations, while 36 patients tested negative. Metastases were detected in the brain in 74 patients, the adrenal glands in 12 patients, bone in 5 patients, vertebrae in 4 patients, and other locations in 12 patients. Radiation therapy for organ metastasis was performed in 81 patients and surgical resection in 27 patients. The 1-year overall survival (OS) rate in these patients was 82.8%, and the 3- and 5-year OS rates were 52.6% and 37.2%, respectively. Patients with positive biomarker test results had 1-, 3-, and 5-year OS rates of 98%, 64%, and 42.7%, respectively. These patients had better OS than those with negative biomarker test results (p=0.031). Patients aged ≤65 years and those with pT1–2 cancers also showed better survival (both p=0.008).
Conclusion: Surgical resection of primary lung cancer is a viable treatment option for selected patients with OM NSCLC in the context of multimodal therapy.

Keywords: Non-small-cell lung carcinoma, Oligometastatic lung neoplasms, Surgical resection, Survival analysis, Mortality

Introduction

Lung cancer remains the most prevalent and fatal type of cancer in Korea, causing 17,980 deaths in 2017 [1]. Non-small cell lung cancer (NSCLC) is the major histological type, constituting approximately 85% of patients with lung cancer, half (46.8%–61.2%) of whom were diagnosed with stage IV disease at their initial diagnosis [2,3]. At stage IV, NSCLC has been considered untreatable; therefore, chemotherapy has principally been considered a therapeutic strategy for palliative care [4]. However, with advances in treatment, including targeted therapy, the survival of patients with stage IV NSCLC has significantly improved [5].

Among patients with metastatic NSCLC, the prognosis for those with a limited number of metastatic lesions (i.e., with oligometastatic [OM] cancer) is more favorable than for those with more extensive spread [6]. Accordingly, some studies have reported aggressive treatment approaches in these patients, including local therapy to eliminate the primary tumors, as well as the metastases [7-15]. This approach has been associated with a 5-year survival rate of approximately 40% [9], higher than the 4% survival

of patients with general stage IV NSCLC who were treated palliatively [16]. However, a significant proportion of patients with OM NSCLC who receive aggressive treatment will contend with the risks of surgery and radiation therapy without benefit. Therefore, more precise strategies to select the patients with OM NSCLC who are likely to benefit from an intention-to-treat approach could significantly improve these treatment outcomes.

This study aimed to evaluate the surgical results of stage IV lung cancer within the context of multimodal therapy.

Methods

Patients

We retrospectively reviewed 117 patients at our center who were diagnosed with stage IV NSCLC before or after surgical resection of the primary lesion, from January 2014 to December 2017. This retrospective study was approved by the Institutional Review Board of Ulsan University College of Medicine (study no., S2022-1978-0001), and prior consent was not required given the retrospective nature of the study. Electronic medical records were reviewed to identify patients diagnosed with stage IV NSCLC.

The study included patients with a pathologist's diagnosis of primary NSCLC with distant metastasis and radical resection or partial resection of the primary lung tumor. All included patients had Eastern Cooperative Oncology Group (ECOG) performance status scores of 2 or less. All patients with bulky N2 or N3 involvement, defined as unresectable lung cancer, were excluded from the analysis. Diagnosis of metastatic lesions was based on imaging tests performed before and after lung resection as part of the preoperative staging, and all patients underwent positron emission tomography (PET) scans. The staging workup usually included PET scans, chest computed tomography (CT), and brain magnetic resonance imaging for all patients with suspected or proven lung cancer. Suspected mediastinal lymph node involvement was verified with endobronchial ultrasound-guided transbronchial needle aspiration or with mediastinoscopy. All patients were classified according to the eighth tumor-node-metastasis (TNM) staging system. A multidisciplinary team discussed all patients to assess the indications and treatment sequences for surgery or adjuvant therapy. Neoadjuvant therapy was performed in patients with unresectable primary lung cancer or patients who required pneumonectomy. Based on the judgment of the oncologists in the multidisciplinary team, adjuvant chemotherapy was generally recommended in all patients with oligometastasis, except those with T1N0 pathology, those >75 years of age, or those in poor physical condition. Four courses of platinum-based systemic chemotherapy were planned for 4–6 weeks postoperatively. After 2008, when the use of targeted therapies began in the treatment of patients with certain biomarkers, such as mutations in the epidermal growth factor receptor (*EGFR*) gene, tyrosine kinase inhibitors became the first-line adjuvant chemotherapy drugs.

Follow-up information on all patients was obtained from their clinical records every 6 months for the first 5 years after surgery and annually thereafter. A chest CT scan was performed at the same time as the clinical visit or when disease recurrence was suspected.

Data collection

The patient characteristics and demographics obtained included sex, age, smoking status, ECOG status, tumor histology, stage, history of adjuvant therapy, type of surgery, presence of biomarkers, location and number of metastatic lesions, and the treatment method for metastatic lesions. Pathological staging was determined using the eighth edition of the TNM classification. The 4 types of surgery included wedge resection, segmentectomy, lobectomy, and pneumonectomy. Postoperative complications were defined as grade 2 or higher if they occurred during hospitalization or readmission within 30 days after surgery, based on the Clavien-Dindo classification [17]. When the biomarker test confirmed mutations in *EGFR*, anaplastic lymphoma kinase (*ALK*), or *ROS1*, the patient was defined as positive.

Statistical analysis

Statistical analysis was performed using R studio ver. 4.2.0 (The R Foundation for Statistical Computing, Vanderbilt University, Nashville, TN, USA). Overall survival included all deaths from any cause during the follow-up period, whereas live patients were right-censored at the last available follow-up. Overall survival in the subgroup analysis was compared by constructing Kaplan-Meier survival curves and comparing them using the log-rank test. Results were presented as hazard ratios and 95% confidence intervals (CI). The significance level was set to 0.05, and 2-sided p-values were calculated for all analyses using R studio version 4.2.0 (The R Foundation for Statistical Computing).

Results

Clinical characteristics

The clinical characteristics of the 117 patients are presented in Table 1. Seventy-three patients (62.4%) were male, and 76 patients (64.9%) were aged <65 years. Based on pathology results, adenocarcinoma was the most frequently diagnosed (97 patients, 82.9%), and squamous cell carcinoma was detected in 14 patients (12%). Of these, 89 patients (76.1%) underwent the biomarker test, and *EGFR*, *ALK*, and *ROS1* mutations were confirmed in 53 patients (45.3%). Twenty-nine patients (24.8%) were diagnosed with T1 disease, 47 patients (40.2%) with T2, 32 patients (27.4%) with T3, and 9 patients (7.7%) with T4. Thirty-three patients (28.2%) were diagnosed with N0 disease, 37 patients (31.6%) with N1, and 47 patients (40.2%) with N2. Additionally, 94 patients (80.3%) underwent lobectomy, 5 (4.3%) underwent segmentectomy, 16 (13.7%) underwent wedge resection, and 2 patients underwent total pneumonectomy (1.7%) (Table 2). In most patients (94.9%), R0 lung resection was achieved. Among the 6 patients (36.8%) confirmed to have intrathoracic R1 resection, the bronchial resection margins were not free in 3 patients, and systemic nodal dissection was incomplete in 3 patients. Consequently, adjuvant therapy was performed in these patients. Neoadjuvant therapy was performed in 11 patients (9.4%), while 76 patients

Table 1. Clinical characteristics of surgically resected patients with stage IV non-small cell lung cancer (N=117)

Characteristic	No. (%)
Sex	
Male	73 (62.4)
Female	44 (37.6)
Age at surgery (yr)	
<65	76 (64.9)
≥65	51 (35.1)
Smoking history	
Yes	72 (61.5)
No	45 (38.5)
ECOG status	
0	69 (59)
1	48 (41)
Clinical T stage	
T1	30 (25.6)
T2	67 (57.3)
T3	15 (12.8)
T4	5 (4.3)
Clinical N stage	
N0	64 (54.7)
N1	25 (21.4)
N2	28 (23.9)
Pathological T stage	
T1	29 (24.8)
T2	47 (40.2)
T3	32 (27.4)
T4	9 (7.7)
Pathological N stage	
N0	33 (28.2)
N1	37 (31.6)
N2	47 (40.2)
Tumor location	
Left lung	53 (45.3)
Right lung	64 (54.7)
Histology	
Adenocarcinoma	97 (82.9)
Squamous cell carcinoma	14 (12)
Others	6 (5.1)
Mutation test	
EGFR/*ALK*/*ROS1* positive	53 (45.3)
EGFR/*ALK*/*ROS1* negative	36 (30.8)
None	28 (23.9)

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Table 2. Combined primary lung surgery and adjuvant treatment for OM-NSCLC and postoperative outcomes (N=117)

Treatment characteristics and outcomes	No. (%)
Surgical approach	
Video-assisted thoracoscopic surgery	70 (59.8)
Thoracotomy or conversion	47 (40.2)
Pulmonary resection	
Wedge resection	16 (13.7)
Segmentectomy	5 (4.3)
Lobectomy	94 (80.3)
Pneumonectomy	2 (1.7)
Pulmonary margin	
R0	111 (94.9)
R1	6 (5.1)
Neoadjuvant therapy	11 (9.4)
Adjuvant therapy	
Chemotherapy	57 (48.7)
Radiation therapy	12 (10.3)
Combined chemotherapy and radiation therapy	17 (14.5)
No treatment	24 (20.5)
Unknown	7 (6)
Postoperative complications	
Respiratory failure	1 (0.9)
Chylothorax	1 (0.9)
Pneumonia	3 (2.6)
Air leakage	1 (0.9)
Postoperative bleeding	1 (0.9)
Postoperative mortality at 30 days	1 (0.9)

OM-NSCLC, oligometastatic non-small cell lung cancer.

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(73.5%) were treated with adjuvant therapy and 24 patients (20.5%) were not treated. Among them, 57 patients were treated with chemotherapy, and biomarker target therapy was administered to patients with confirmed mutations. Of the 24 patients (20.5%) who did not receive adjuvant therapy, 16 patients were diagnosed as pT1N0 and therefore did not receive treatment, and 1 patient was excluded due to in-hospital mortality. Seven patients were ≥75 years old or were in poor physical condition and did not undergo chemotherapy. Seven patients (6%) declined further treatment. One in-hospital death, attributed to acute respiratory distress syndrome, occurred after surgery (within 30 days). One patient (0.9%) underwent reoperation for postoperative bleeding.

Table 3. Metastatic sites and treatment characteristics in OM-NSCLC (N=117)

Metastases characteristic	No. (%)
Metastatic sites	
1–3 Brain metastases	73 (62.4)
Adrenal gland	12 (10.3)
Bone	15 (12.8)
Vertebrae	4 (3.4)
Liver	2 (1.7)
Others	7 (6)
Multiple metastases	4 (3.4)
Local therapy in metastasis	
Gamma knife/LINAC/SRS	81 (69.2)
Surgery	27 (23.1)
Local therapy not used	3 (2.6)
Unknown	6 (5.1)

OM-NSCLC, oligometastatic non-small cell lung cancer; LINAC, linear accelerator; SRS, stereotactic radiosurgery.

Brain metastasis was the most common location of metastasis (73 patients, 62.4%), followed by adrenal metastasis (12 patients, 10.3%), and bone metastasis (15 patients, 12.8%). Metastasis was treated with radiation therapy in 91 patients (69.2%) and surgical resection in 27 patients (23.1%). Three patients (2.6%) did not receive additional treatment for metastasis, and the information for 6 patients (5.1%) could not be identified (Table 3).

Overall survival results

The median duration of survival was 2.9 years (95% CI, 1.48–5.84 years), and the OS rates at 1, 3, and 5 years were 82.8%, 52.6%, and 37.2%, respectively (Fig. 1). Subgroup analysis showed 1-year, 3-year, and 5-year OS rates of 88%, 60.8%, and 44.4%, respectively, in patients <65 years and

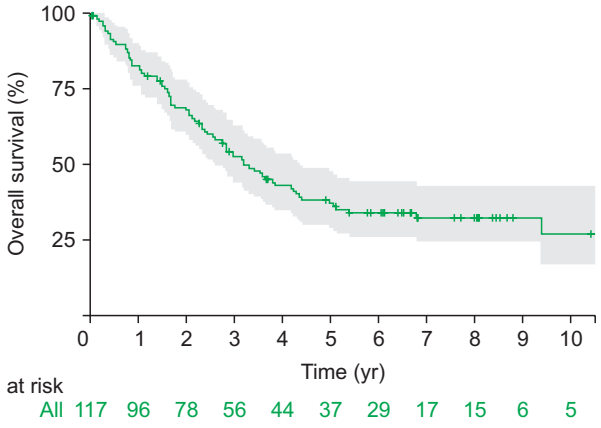

Fig. 1. The Kaplan-Meier analysis of overall survival after surgery in patients with oligometastatic non-small cell lung cancer.

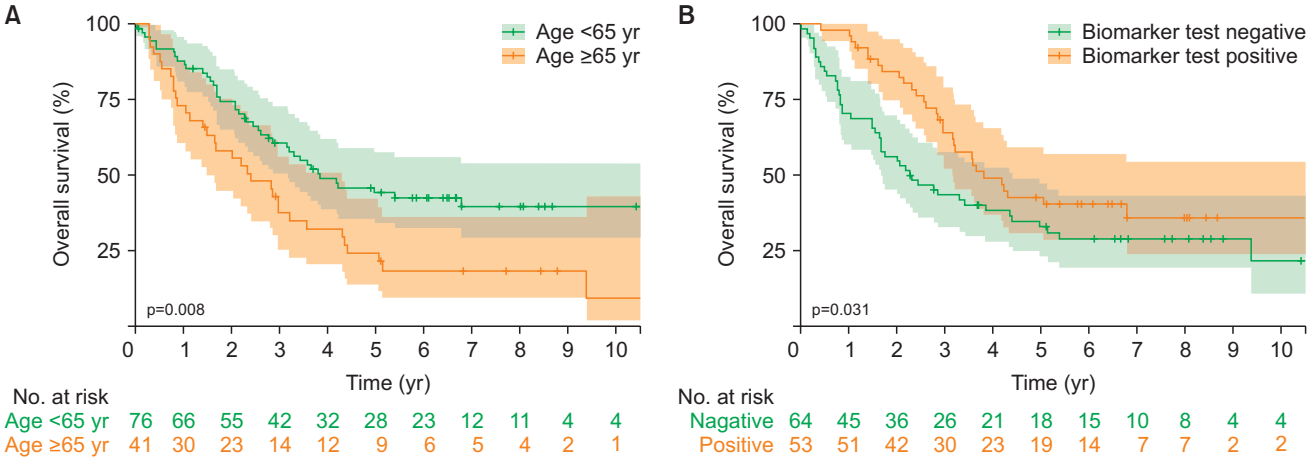

Fig. 2. Kaplan-Meier survival analysis based on age (A) and biomarker (epidermal growth factor receptor, anaplastic lymphoma kinase, or *ROS1*) positivity (B) in patients with oligometastatic non-small cell lung cancer.

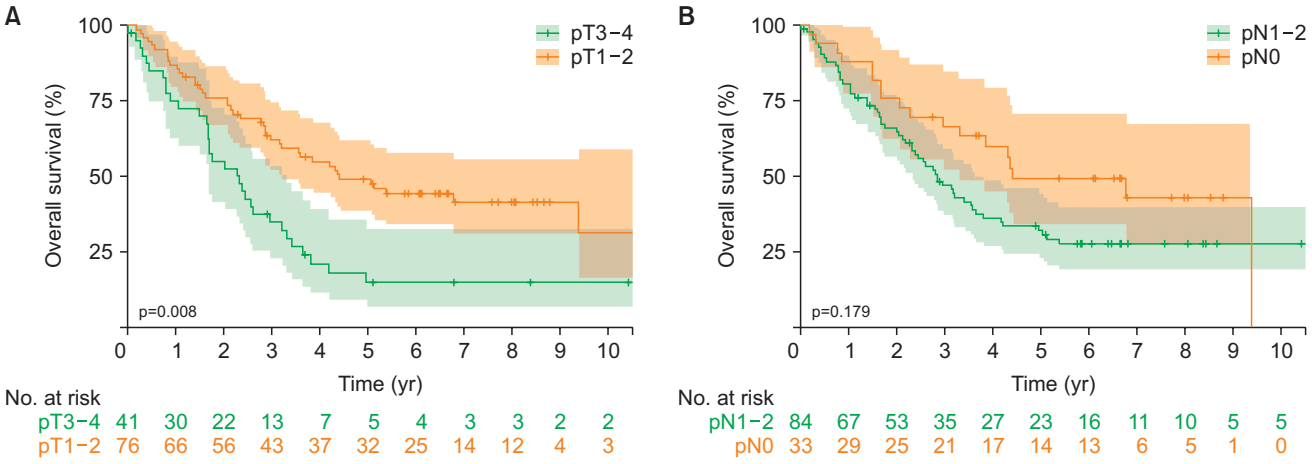

Fig. 3. The Kaplan-Meier survival analysis for oligometastatic non-small cell lung cancer patients with pathological (p)T1–2 versus pT3–4 disease (A) and patients with N0 versus pN1–2 disease (B).

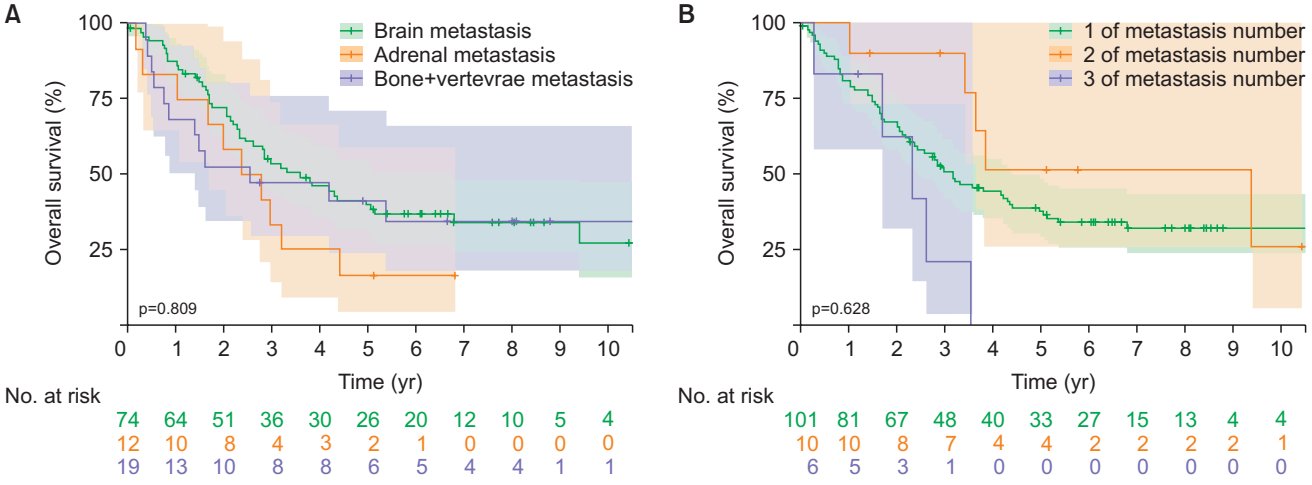

Fig. 4. The Kaplan-Meier survival analysis for patients with oligometastatic non-small cell lung cancer, based on the site of metastasis: brain, adrenal, bone and vertebrae (A) and the number of metastases (B).

73.1%, 37.6%, and 24.2%, respectively, in those aged ≥65 years (p= 0.008) (Fig. 2A). Kaplan-Meier analysis showed that positive biomarker tests influenced the survival rate. In the biomarker-positive patient group, the 1-year, 3-year, and 5-year survival rates were 98%, 64%, and 42.7%, respectively, while they were 70.3%, 43.5%, and 32.8% in those testing negative (p=0.031) (Fig. 2B). Patients with pathological T1–2 NSCLC had better OS rates than those with pathological T3–4 disease. The estimated 1-year, 3-year, and 5-year OS rates were 86.8%, 62.2%, and 49% in the T1–2 group and 75%, 34.8%, and 15.1% in the T3–4 group, respectively (p=0.008) (Fig. 3A). However, positive node (N) pathology did not significantly influence survival time (p=0.179) (Fig. 3B). The OS rate of patients with adrenal metastasis was lower than that of those with brain metastasis or other metastatic lesions after 2 years (p=0.809) (Fig. 4A). Neither the location nor the number of metastatic lesions significantly affected OS (p=0.628) (Fig. 4B).

Discussion

The term oligometastasis, first proposed by Hellman and Weichselbaum [18], defines the intermediate-state tumor metastasis process in the changeover period between localized primary tumor and extensive metastases and involves <5 metastases, limited to 1 organ, which can be treated locally [19]. Since the number of NSCLC patients with OM is limited, the treatment strategies are still inconclusive. The

National Comprehensive Cancer Network guidelines in 2019 suggested that treatment should include local metastasis treatment followed by a combination of lung resection with chemotherapy (before or after surgery) in patients with a single brain or adrenal metastasis and a primary tumor that is T1–2/N0–1 or T3/N0. In validation of these guidelines, Yang et al. [20] reported that 5-year OS rates in the National Cancer Database analysis were 28.8% for stage T1–2/N0, 20.5% for stage T3–4/N0 and 17.4% for stage T1–2/N1. For patients with OM NSCLC, more active treatment may lead to a better survival rate.

A systematic review published in 2013 reported that the 5-year OS rate for patients treated for OM was 8.3%–86% [21]. However, even across these studies, control of the primary tumor was considered to significantly affect survival and determine prognosis. In our study, the 5-year OS rate of patients who underwent surgical resection of the primary tumor was 42.7%, and the median survival time was 2.91 years. We focused on patients undergoing lung resection and radical local treatment for metastatic lesions. Overall, our population was younger and likely in better clinical condition than the average population with NSCLC because of the indications for anatomical lung resection and criteria for surgery as discussed in our multidisciplinary setting. The best survival outcomes were obtained in younger patients. In a subgroup analysis, using comparative Kaplan-Meier analysis, there was a significant difference between patients <65 years and patients ≥65 years, confirming the findings of other studies with patient groups >60 years old [13,22].

The other factor strongly associated with OS in our study was pathological staging of T1–2 in the primary tumor. Endo et al. [9] reported that patients with clinical T1–2N0–1 NSCLC with OM lesions were good candidates for surgical resection, with an expected 5-year survival rate of approximately 40%. In our study, survival was significantly associated with the T stage. Moreover, surgical treatment showed significantly better OS rates in patients with OM NSCLC who were diagnosed with T1–2 disease, with a 5-year survival rate of approximately 49%. Many other studies have shown significant differences in survival rates according to an N positive or N2 stage [11,14]. However, the clinical and pathological results did not differ significantly in our study. This can be considered a source of bias given the clinical understating of diagnoses of pathological N2 rather than clinical N2. Further research in a wider patient population is needed.

Moreover, patients confirmed as positive in the biomarker study were able to proceed with targeted therapy, and according to analysis of these results, the 5-year survival rate was significantly higher at 42.7%. In addition, Park et al. [23] reported that the survival rate improved significantly when surgical resection was performed after targeted treatment. Several studies have shown that targeted therapy significantly affects the OS rate of lung cancer [24], and the biomarker positivity in our study suggests this is also true in OM NSCLC. In the biomarker study, an endobronchial ultrasound-assisted mediastinal biopsy was performed before surgery to confirm the results. Currently, when targeted therapy is deemed possible, a significant survival rate can be expected and actively proceeding with surgical treatment in patients with OM NSCLC is recommended. However, the prognosis can be predicted based on postoperative pathology results in patients who have not been diagnosed before surgery; thus, other factors must be considered in multidisciplinary settings when determining surgery.

Our study had several limitations. First was the single-center, retrospective design of the study. Moreover, population selection bias occurred. We only included patients who underwent surgical resection of the primary tumor, the characteristics of which were not truly representative of the general population of patients with stage IV NSCLC. The analysis of pathological staging was a limitation because it did not provide information that would be relevant before treatment. However, since the study results were compatible with the true staging of the disease, invasive preoperative staging is strongly recommended when considering lung resection in patients with OM NSCLC.

In conclusion, we demonstrated that surgery could provide a favorable prognosis with low mortality in selected patients with OM stage IV NSCLC. Furthermore, with the development of targeted NSCLC therapies, our results may support synergistic strategies, including surgery, to reduce the burden of mutational tumors, even in more advanced cases. Thus, surgery for primary lung tumors should be considered in selected patients with NSCLC with OM disease.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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