

Long-Term Treatment-Free Survival After Multimodal Therapy in a Patient with Stage IV Lung Adenocarcinoma

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Abstract: We report the first case of a patient with non-small cell lung cancer (NSCLC) with malignant pleural effusion (MPE) who achieved disease- and treatment-free survival for nearly 10 years. A 50-year-old man was diagnosed with NSCLC with MPE and underwent chemotherapy and salvage thoracic surgery. The patient received chemotherapy with cisplatin, pemetrexed, and bevacizumab, and a partial response was achieved. After informed consent was obtained from the patient, right middle lobectomy was performed to achieve local tumor control. Postoperative adjuvant chemotherapy with pemetrexed and bevacizumab was discontinued after almost 1 year of chemotherapy due to side effects such as diarrhea and muscle weakness. The patient has survived without recurrence of lung cancer for more than 11 years after being diagnosed and nearly 10 years after discontinuing chemotherapy.

Keywords: malignant pleural effusion, bevacizumab, pemetrexed, salvage surgery, cure

Introduction

Lung cancer remains the leading cause of cancer-related death worldwide.¹ Even with the best available therapies, patients with stage IV lung cancer have a poor prognosis and are generally believed to be incurable.² According to the site and number of distant metastases, stage IV lung cancer is classified into M1a, M1b or M1c, based on the TNM classification of the Union of International Cancer Control (UICC), 8th edition.³ Additionally, the median overall survival between M1a, M1b and M1c is significantly different (M1a: 11.5 months, M1b: 11.4 months, and M1c: 6.3 months).^{4,5}

Most clinical guidelines for lung cancer recommend systemic therapy; surgical resection or radical radiation therapy aimed at cure are not recommended in patients with lung cancer with distant metastasis.^{6,7} Stage IV lung cancers with a specific characteristic referred to as “oligometastasis” (often classified as stage IV with M1b) have attracted attention recently because multimodal therapies, including local radical therapy, have improved survival and almost achieved cure in clinical trials.^{8,9} However, patients with malignant pleural effusion (MPE) whose cancers are classified as stage IV with M1a are not considered oligometastatic by consensus guidelines^{9,10} since cancer cells are disseminated into the intrathoracic space and cannot be removed completely by local therapy.¹¹

Here, we report the case of a patient with non-small cell lung cancer (NSCLC) with MPE treated with multimodal therapy and survived without a recurrence for more than 11 years after diagnosis and 10 years after discontinuing cancer treatment.

Case Presentation

A 50-year-old Japanese man developed dry cough beginning in February 2010. A chest X-ray during a medical checkup in June 2010 showed a 20-mm nodule in the right lung, and a chest computed tomography (CT) scan in July 2010 showed a 26 mm nodule in the medial segment of the middle lobe, a right pleural effusion, and scattered nodules in the interlobar pleura (Figure 1A and B). Lung cancer was suspected, and the patient was referred to the Department of Respiratory Medicine at our hospital for further examination in July 2010.

A whole body ^{18}F -FDG (^{18}F -fluorodeoxy-glucose) positron emission tomography (PET)-CT demonstrated high FDG uptake in the lung nodule on the medial segment. The maximum standardized uptake value (SUVmax) was 6.1 (Figure 1C). Gadolinium-enhanced brain magnetic resonance imaging and bone scintigraphy showed no other metastases.

Biopsy of the lung nodule from the medial segment obtained by bronchoscopy and cytology of the pleural fluid obtained by thoracic puncture confirmed lung adenocarcinoma (Figure 2). The tumor was classified as clinical T1cN0M1a, which is stage IVA according to the TNM classification of the UICC, 8th edition. The patient's previous medical history was unremarkable except for being a past light smoker (1 pack-years). The Eastern Cooperative Oncology Group performance status (ECOG-PS) at the time of admission was 0. Lung tissue samples showed no mutations in the epidermal growth factor receptor (*EGFR*) by

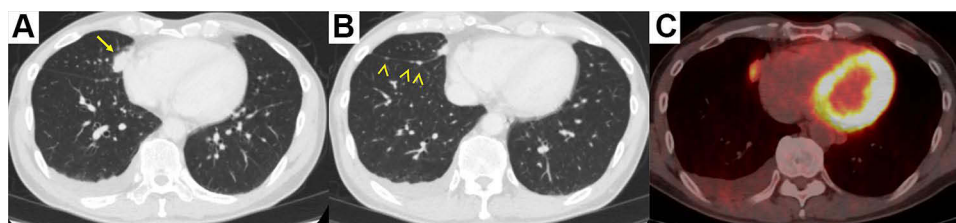


Figure 1 CT scan and ^{18}F -FDG PET-CT. CT scans (A and B) and ^{18}F -FDG PET-CT (C) at initial diagnosis. (A) The nodule in the right middle lobe indicated by an arrow was the primary lesion of the lung cancer. (B) Scattered nodules in the interlobar pleura indicated by arrows were disseminated lesions. Right pleural effusion was detected in both images. (C) FDG uptake at the nodule in the right middle lobe was high, the maximum standardized uptake value was 6.1.

Abbreviations: CT, computed tomography; FDG, fluorodeoxy-glucose; PET, positron emission tomography.

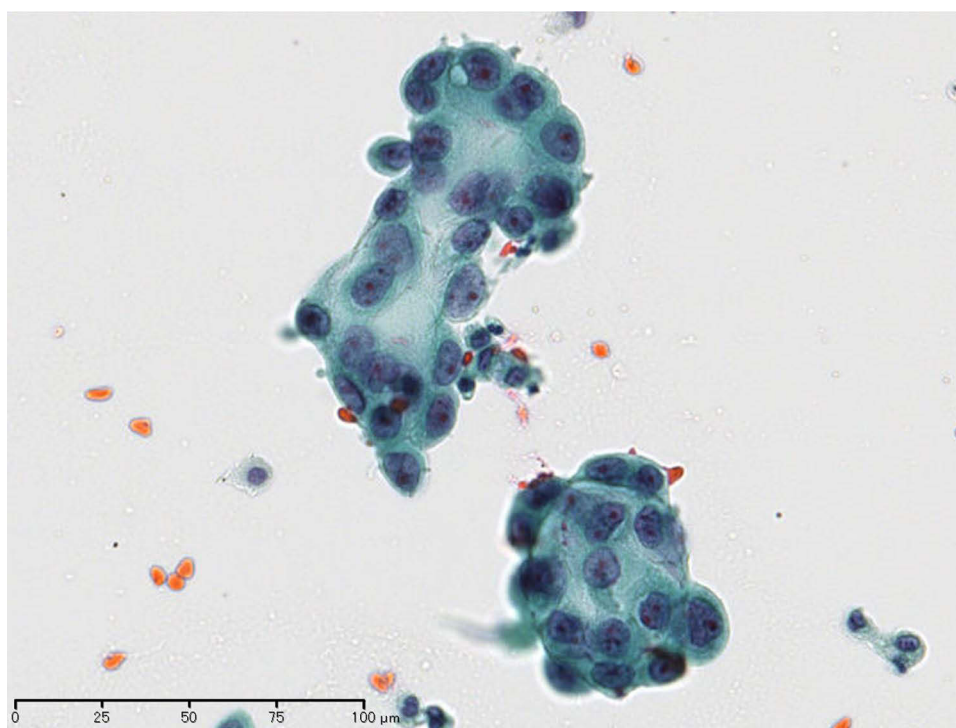


Figure 2 Cytological examination of pleural effusion. The pleural effusion was positive for adenocarcinoma cells (scale bar: 100 μm).

the peptide nucleic acid-locked nucleic acid PCR clamp.¹² The carcinoembryonic antigen (CEA) level was 18.1 ng/mL (normal, 0–5 ng/mL). Beginning in August 2010, the patient received cisplatin (75 mg/sq), pemetrexed (PEM, 500 mg/sq), and bevacizumab (BEV, 1000mg/body) as first-line chemotherapy. After 4 cycles of chemotherapy, the tumor size decreased to 1 cm in diameter, and pleural effusion had disappeared; the 61.5% reduction in tumor size indicated that partial response was achieved according to the Response Evaluation Criteria in Solid Tumors version 1.1 (Figures 3A and B). PET-CT revealed that FDG uptake was negative in the tumor (Figure 3C). The tumor marker CEA levels decreased to 2.4 ng/mL, which was within the normal range (Figure 4).

The treatment strategy was debated at the multidisciplinary lung cancer board conference since the patient's strong will for additional local treatment of the residual tumor on CT imaging. Finally, surgery was selected with the patient's consent to remove the residual tumor and achieve local tumor control. Surgical findings in the thoracic cavity included a tumor on the mediastinal area of S5 with a mild pleural depression and white nodules that were mainly observed on the interlobar surfaces of the lower, middle, and upper lobes and appeared to be scars of healed pleural dissemination; no similar white nodules were found on the diaphragmatic or mural pleura. The white nodule on the interlobar surface of S8 was partially removed and submitted for frozen section examination, which showed no evidence of malignancy. Rapid pathological diagnosis of the enlarged hilar lymph nodes in the middle lobe using pleural lavage cytology was also negative for malignancy. Finally, surgical resection of the right middle lobe and mediastinal lymph node dissection were performed.

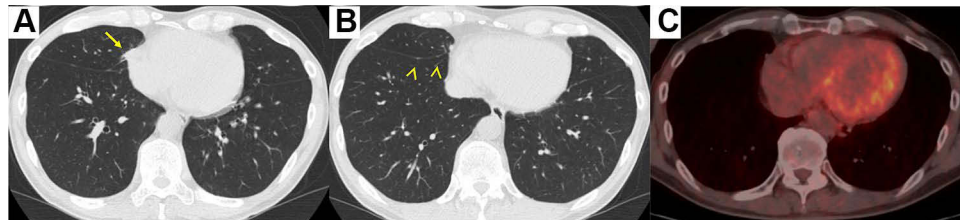


Figure 3 CT scan and 18F-FDG PET-CT after treatment with 4 cycles of cisplatin, pemetrexed, and bevacizumab. (A and B) The nodule in the right middle lobe indicated by an arrow (A) and the nodules in the interlobar pleura indicated by arrows (B) decreased in size, and the right pleural effusion resolved after treatment. (C) FDG uptake was negative at the reduced nodule after treatment.

Abbreviations: CT, computed tomography; FDG, fluorodeoxy-glucose; PET, positron emission tomography.

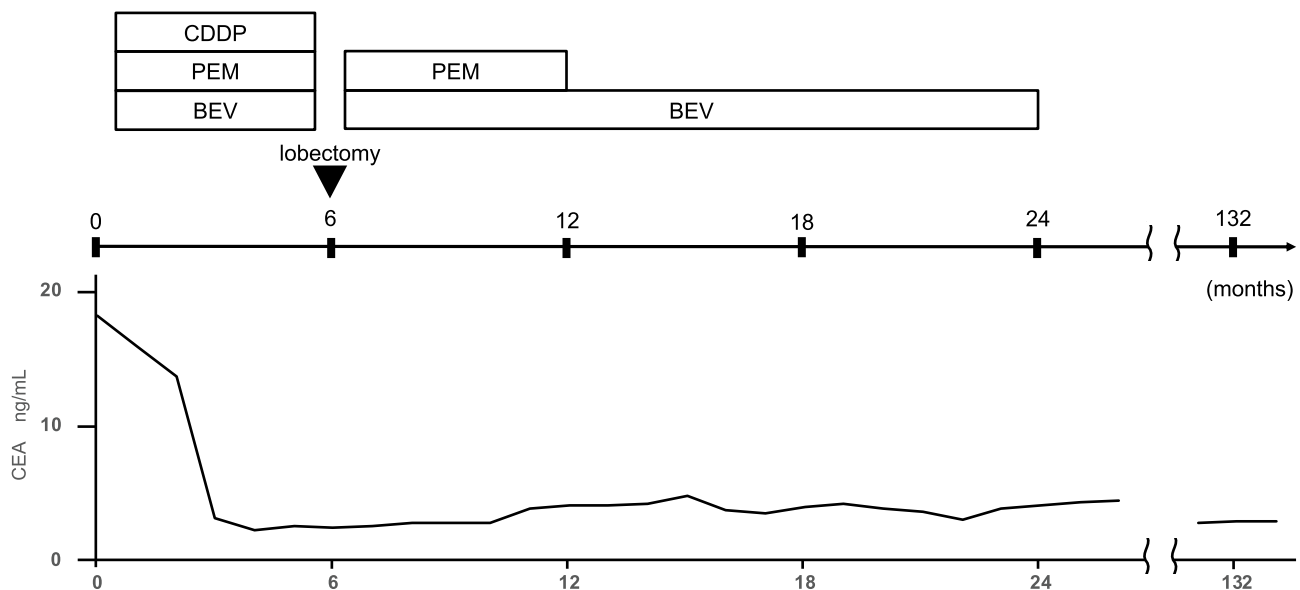


Figure 4 Time course of treatment and laboratory findings.

Abbreviations: CDDP, cisplatin; PEM, pemetrexed; BEV, bevacizumab; CEA, carcinoembryonic antigen.

Macroscopic examination of the specimen from the right middle lobectomy revealed that the tumor nodule became a fibrotic lesion adjacent to the pleura (Figure 5A). Upon histological examination, solid tumor cell clusters were observed among lung tissue with collapsed alveoli and fibroelastosis (Figures 5B and C). Immunohistochemical staining of the tumor cells was positive for TTF-1, and approximately 5% were positive for Ki-67. Hence, the tumor cells were diagnosed as residual adenocarcinoma (Figures 5D and E). The tumor bed measured 20×5 mm and included the viable tumor (5%) and stroma (95%) without necrotic area. No viable tumor cells were observed in the pleura. Additionally, low-volume metastasis in the #7 lymph node was confirmed by histological examination (Figure 5F). These results show that the effect of chemotherapy on the primary site was equivalent to a major pathologic response according to the neoadjuvant therapy criteria.¹³

Pathological staging revealed that the tumor was ypT1aN2M0, stage IIIA. After surgery, the patient received 6 cycles of PEM and BEV as adjuvant chemotherapy and 12 additional cycles of BEV until May 2012. Chemotherapy was discontinued in June 2012 due to fatigue and muscle weakness, although it was unclear whether these symptoms were caused by the drugs.

As of February 2022, the patient has been alive for more than 11 years without disease recurrence after being diagnosed with stage IV NSCLC with MPE. Furthermore, the patient has not received any anti-cancer treatments in over 10 years.

Discussion and Conclusion

Stage IV lung cancer has a high mortality rate. Its 5-year overall survival rate is below 10%, although expected survival times have increased with recent advances in treatment methodology.^{2,14,15}

Several studies have reported factors associated with the long-term survival of patients with advanced stage NSCLC,^{16–22} including a good ECOG-PS, positive EGFR mutation status, absence of extra-thoracic lesions, and elevated tumor-infiltrating lymphocyte levels (Table 1). Generally, local therapies aimed at radical cure are not indicated for stage

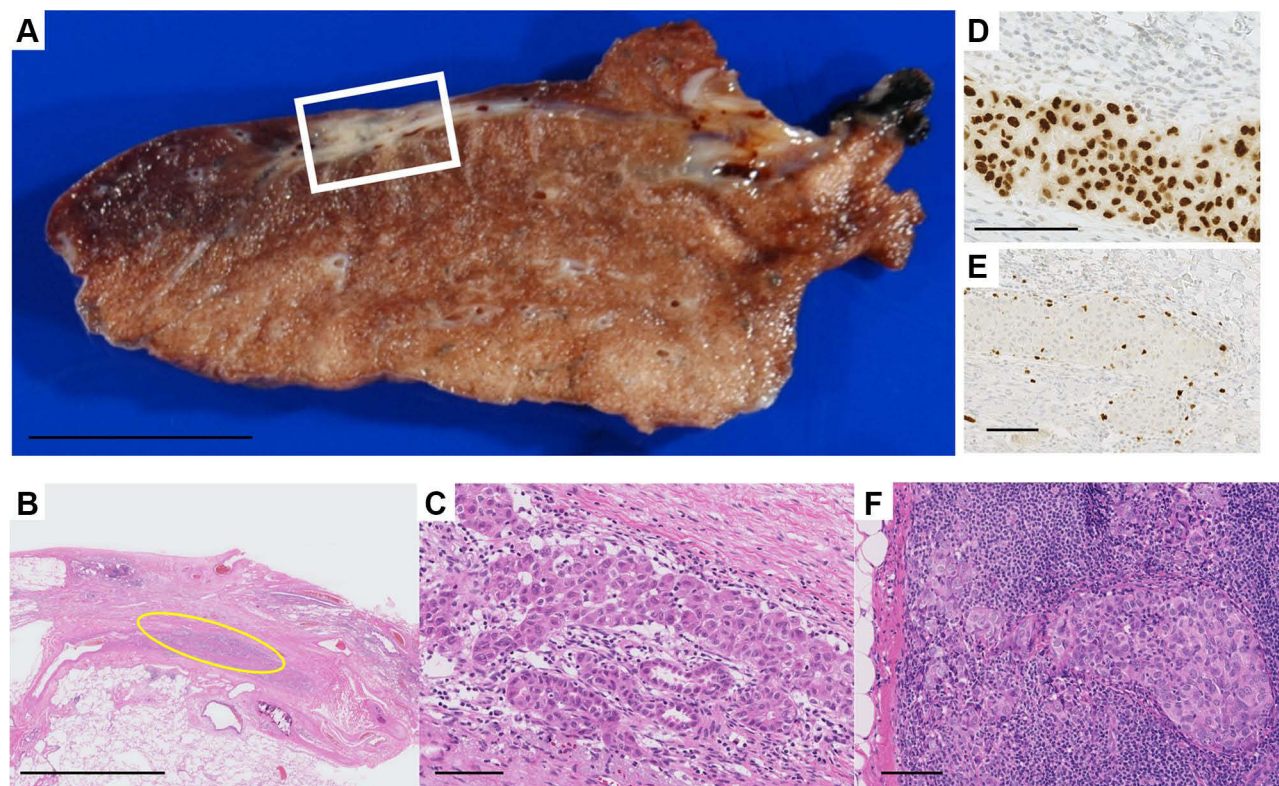


Figure 5 Histological examination of surgical specimens. (A) Gross findings of the resected right middle lobe revealed the residual tumor as a fibrotic nodule indicated by the white square (scale bar: 2 cm). (B) Histological findings at low power revealed alveolar collapse, fibrosis, and some tumor cell clusters with no exposure to the pleural surface indicated by the yellow ellipse (scale bar: 2 mm). (C) Histological examination of atypical cells with nuclear enlargement at high power consistently showed adenocarcinoma (scale bar: 100 μ m). (D) Immunohistochemical staining revealed that tumor cells were positive for TTF-1 (scale bar: 100 μ m). (E) Immunohistochemical staining revealed that 5% of the tumor cells were positive for MIB-1 (scale bar: 100 μ m). (F) Lymph node metastasis in the #7 lymph node of the surgical specimen (scale bar: 100 μ m).

Abbreviation: TTF-1, thyroid transcription factor-1.

Table I Cases of Advanced Non-Small Cell Lung Cancer with Long-Term Survival from the Literature

Author	Year	Stage	Number of Patient			Good Prognostic Factors
			Total	>2-Year Survival (%)	>5-Year Survival (%)	
Okamoto ²¹	2005	IV	222	17(7.7)	3(1.4)	Early Node status
						Single metastatic site
						Good performance status
						Surgery for initial therapy
Kaira ¹⁶	2010	IIIB, IV	124	34(27.4)	10(8.1)	Good performance status
						Adenocarcinoma
						EGFR-TKI therapy
Leprieur ²⁰	201	IIIB, IV	245	39(15.9)	1(0.41)	Good performance status
						Surgery
						Maintenance treatment
						First progression after >3months
						Greater number of chemotherapy lines
						LDH <500 IU/L
Hirashima ¹⁹	2014	IV	268	48(17.9)	22(8.2)	Good response to 1st line chemotherapy
						EGFR-TKI therapy
						Continuing effective cytotoxic regimens
						Radiotherapy as local therapy
Huang ¹⁷	2018	IV	1030	NA	52(5.0)	Younger than 60 years old
						Absence of extrathoracic spread
						EGFR-TKI therapy
Davis ²²	2019	IV	44387	NA	1014(2.3)	Younger age
						Lower Tumor status
						Surgery

Abbreviations: NA, not assessed; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; LDH, lactate dehydrogenase.

IV lung cancer patients.² However, Aoki et al reported that 80% of patients diagnosed with stage IV lung cancer but achieved complete remission received local radical therapy such as surgery or radiation during treatment, though this complete remission does not directly mean improving their survival.¹⁸ This suggests that radical local therapy as a part of comprehensive multimodal treatment could benefit selected patients with stage IV lung cancer to achieve complete remission. In the present case, there was a small size of residual alive tumors in a surgical specimen of primary tumor and lymph node metastasis. Meanwhile, multiple clinical trials have reported that additional local radical therapy can improve prognosis in patients with stage IV lung cancer with oligometastasis and good ECOG-PS, although results from large-scale prospective clinical trials are not yet available.⁹

As previously mentioned, local radical therapy is not generally indicated for patients with lung cancer with MPE, as they are not recognized as having an oligometastatic disease. However, a potential benefit of local treatment, such as surgery, has been reported in patients with MPE and/or malignant pleural nodules in previous studies^{23–33} (Table 2). For example, Aoki et al reported a few cases. Aoki et al also reported a few similar long-term survivors without cancer treatment in patients with stage IV lung cancer.¹⁸ Additionally, several studies reported the effectiveness of hyperthermic intrathoracic chemotherapy (HITHOC) that it can control the symptoms and prolong the survival of patients with MPE.³⁴ Surgery combined with HITHOC has been recently reported to be an effective surgical intervention for selected pM1a patients to prolong life expectancy. A systematic review reported by Migliore et al³⁵ showed favorable outcomes for N0–I NSCLC patients with MPE undergoing primary tumor resection plus HITHOC with a median survival time of 18 months and 2-year overall survival of 28.5%. The status of lymph node metastasis in surgical specimens has repeatedly been reported as a significant prognostic factor, and it has been demonstrated that patients with positive N2/3 lymph node metastasis have significantly worse outcomes than those with or without N1 lymph node metastasis.^{23,24} However, there is a large variation among the 5-year survival rates and mean survival times reported in these studies, and it is therefore difficult to determine which cases with MPE could undergo surgery.

In the present case, we used radical surgery when the patient achieved induced oligometastatic status after systemic chemotherapy. Induced oligometastatic status is defined as the presence of multiple metastatic lesions at the time of diagnosis that are reduced by effective treatment as they are detected only as a limited disease. It has not been determined whether additional local therapy would improve patients' prognosis following the achievement of induced oligometastatic status. After surgery, a histological examination revealed residual cancer cells in the resected mediastinal lymph node #7, which was defined as the N2 lymph node.

Table 2 Summary of Studies Reporting Surgically Treated Patients with Malignant Pleural Disease

Author	Year	Number of Patient	Survival		Good Prognostic Factors
			MST (Months)	5-Year (%)	
Kodama ²⁹	1993	31	NA	24.6	Early Node status
Ohta ³¹	2000	43	17	13.1	Adenocarcinoma
Ichinose ²⁸	2001	100	20.6	22.8	Early Node status
					Female
Shiba ³²	2001	65	NA	14.3	Low Ki-67 labeling index
					Early Node status
					No tumor differentiation
Fukuse ²⁷	2001	49	15	15.6	No pleural dissemination
					Early Tumor status
Mordant ³⁰	2011	32	15	16.2	Node 0
Okamoto ²³	2012	73	25.9	23.7	Early Node status
Iida ²⁴	2015	313	34	29.3	Good performance status
					Early Node status
					No macroscopic residual tumor
Ren ²⁶	2016	83	NA	16.8	Primary tumor resection
					No pleural effusion
					Early Node status
					Adenocarcinoma

Abbreviations: MST, median survival time; NA, not assessed.

We believe that salvage surgical resection was potentially beneficial to achieving treatment-free survival in this patient, as Davis et al reported²² in their large retrospective study that in addition to a younger age and lower T status, surgery was a good prognostic factor for long-term survival in 44,387 patients with stage IV lung cancer. Although the necessity of adjuvant chemotherapy was controversial in this case, based on previous reports, the risk of recurrence seemed high due to the presence of lymph node metastases in the surgical specimen.^{23,24,26,28,29,32,33} Given that the preoperative chemotherapy effectiveness is limited in adenocarcinomas,³⁶ we selected pemetrexed and bevacizumab for adjuvant chemotherapy, as administration of these drugs before surgery resulted in a remarkable reduction of the tumor size on pathological evaluation. This is a rare case with stage IV NSCLC with MPE and N2 lymph node metastasis, who survived for more than 11 years after surgery without relapse. It is difficult to conclude whether surgery is a good option in patients with stage IV lung cancer who achieve a similar induced oligometastatic status. Little is known about the significant factors that contribute to improved prognosis and survival rates that approach those of remission in stage IV lung cancer patients. To elucidate the mechanisms to achieve treatment-free survival in patients with stage IV lung cancer, it is necessary to document similar cases. The number of cases with induced oligometastatic status is expected to increase with the recent approval of promising new drugs (eg, drugs that target driver genes and immune checkpoint inhibitors), and evidence from prospective trials will be required to further evaluate these cases.³⁷

Abbreviations

UICC, Union of International Cancer Control; NSCLC, non-small cell lung cancer; MPE, malignant pleural effusion; CT, computed tomography; FDG-PET, ¹⁸Fluorodeoxyglucose positron emission tomography; ECOG-PS, the eastern cooperative oncology group performance status; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; HITHOC, hyperthermic intrathoracic chemotherapy.

Ethics Approval and Informed Consent

This study was approved by the ethical review boards of Keio University School of Medicine (approval no. 20110171).

Consent for Publication

Written informed consent was obtained from the patient to publish this case report and any accompanying images.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

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