

Clinical Characteristics and Therapeutic Outcomes of Metastatic Peritoneal Carcinomatosis in Non-Small-Cell Lung Cancer

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Background: Metastatic peritoneal carcinomatosis (MPC) is not common in patients with non-small cell lung cancer (NSCLC), and the clinical characteristics and treatment outcomes are still unclear.

Patients and Methods: We recruited 46 NSCLC patients with MPC at Keio University and affiliated hospitals (Keio Lung Oncology Group) between January 2011 and December 2017, then retrospectively investigated their clinical characteristics and the impact of treatment interventions on their survival.

Results: The profile of histological subtype was predominantly adenocarcinoma and 15 patients harbored driver oncogenes. Univariate and multivariate analysis demonstrated that performance status and the presence of a driver oncogene were significantly associated with the prolonged overall survival (OS). Regarding treatment, the median OS in the treatment group (9.3 months) was significantly longer than in the best supportive care group (1.3 months) ($P < 0.0001$).

Conclusion: The prognosis of MPC in NSCLC patients who receive only the best supportive care is poor, but therapeutic intervention may improve prognosis.

Keywords: metastatic peritoneal carcinomatosis, NSCLC, EGFR, malignant ascites, peritoneal nodule, intraperitoneal dissemination

Introduction

Lung cancer remains a deadly disease despite the recent development of more effective treatments.¹ Morbidity and mortality in non-small lung cancer (NSCLC) is worsened by metastasis to extrapulmonary organs such as brain, bone and liver.² Metastases not only shorten prognosis, but also compromise quality of life (QOL).³ In recent years, many treatment modalities for NSCLC have been developed, including molecularly targeted agents and immune checkpoint blockade, and these approaches have improved therapeutic options for patients with metastases. Recent trials have emphasized treatment strategies for NSCLC brain metastasis and intrathoracic dissemination, along with malignant pleural effusion.⁴⁻⁶ On the other hand, metastatic peritoneal carcinomatosis (MPC) is not a common NSCLC complication in daily practice.⁷ Since previous studies have reported that patients with MPC have worse QOL including various symptoms such as poor appetite, shortness of breath, nausea, abdominal pain, and general weakness,⁸ it is generally thought among oncologists that the prognosis of NSCLC with MPC is poor. Palliative therapy can relieve these symptoms, but adequate treatment strategies have not yet been developed. One of the reasons for disappointing outcomes with MPC may be that thoracic oncologists lack experience in treating peritoneal complications. However, at

autopsy, metastasis to the peritoneum from lung cancer is not a rare finding.⁸ In addition, recent developments in medical diagnostics increase opportunities to detect MPC in NSCLC patients. In this multicenter study, we identified over 40 NSCLC patients with MPC and retrospectively investigated their clinical course. As a result, we clarified clinical characteristics of MPC which were associated with poor prognosis and evaluated the impact of therapeutic intervention on their prognosis.

Materials and Methods

NSCLC patients with MPC were recruited at Keio University and affiliated hospitals (Keio Lung Oncology Group) between January 2011 and December 2017.

MPC was defined as malignant ascites by cytologic pathology or a radiographic finding of peritoneal nodules ≥ 10 mm reflecting intraperitoneal dissemination. Eligible criteria were as follows: patients who were, (1) histologically or cytologically diagnosed with NSCLC, and (2) simultaneously or subsequently accompanied by MPC.

The following clinical data were collected from medical records: dates when lung cancer and MPC were diagnosed, age at the time of lung cancer diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), histology, smoking status, *EGFR/ALK* mutation status, treatment data, and survival data.

Statistical Analysis

Statistical analysis using Fisher's exact test was performed to evaluate clinical characteristics. Kaplan–Meier method with log rank test was used to compare survival. Cox proportional hazards model was conducted for multivariate analysis of prognostic factors. $P < 0.05$ was considered statistically significant for all tests. Staging was according to the 8th edition of the Union for International Cancer Control TNM classification.

This study was approved by the ethical review board committee of Tachikawa Hospital, Keio University and affiliated hospitals for the use of an opt-out style covering patient data confidentiality, and conducted in accordance with the 1964 Declaration of Helsinki, as revised in 2013. The requirement to obtain informed consent was waived because of the retrospective design.

Results

Clinical Characteristics of the Study Participants

Baseline patient characteristics at MPC diagnosis are summarized in Table 1. In total, 46 patients met inclusion criteria and their median age was 66 years. Of them, 33 and 36 were male and current/former smokers, respectively (71.7%, 78.3%).

Table 1 Patient Characteristic

	No. of Patients
Total enrolled	46
Age (years) Median (range)	66 (IQR 59–71)
Sex Male Female	33 13
PS 0/1/2/3/4	5/17/10/11/3
Histology Adenocarcinoma Pleomorphic carcinoma Adenosquamous NSCLC-NOS	40 1 1 4
EGFR/ALK mutations Positive Negative/unknown	15 31
Smoking Status Former or current Never	36 10
Onset of MPC Initial Late	12 34
Type of MPC Peritoneal nodules Malignant ascites Both	31 4 11
Ascites mutation status Driver oncogene positive Driver oncogene negative Not examined	4 3 8
Malignant pleural effusions Positive Negative/unknown	17 29
Brain metastasis Positive Negative	5 41

The profile of histological subtype was predominantly adenocarcinoma ($n = 40$, 87.0%). Fifteen patients harbored driver oncogenes (32.6%): 14 *EGFR* mutations and 1 *ALK* fusion rearrangement. Twelve (26.1%) were diagnosed with MPC at the same time with the diagnosis of NSCLC, and 34 (73.9%) were subsequently diagnosed with MPC. Thirty-one were determined to have MPC based on radiographic findings (67.0%). Seventeen (37.0%) and 5 patients (11.0%) had malignant pleural effusion (MPE) and brain metastasis at MPC diagnosis, respectively. Ascites cytology tests successfully detected 4 *EGFR* mutation from 7 patients whose tumor specimen had previously harbored the mutation.

Clinical Course of MPC

Median overall survival (OS) after MPC diagnosis was 5.2 months in all patients (95% Confidence interval 2.1–6.3) (Figure 1A). Log rank test revealed that good PS (0 or 1) and the presence of a driver oncogene were significantly

associated with prolonged OS (Table 2). Median OS in the poor PS group (2 or more) was remarkably shorter than in the good PS group (1.8 months vs 13.1 months, hazard ratio, 11.2; 95% CI, 4.86–25.8) (Figure 1B). The presence or absence of a driver oncogene led to OS of 12.9 months and 2.5 months, respectively (hazard ratio, 0.41; 95% CI, 0.21–0.81) (Figure 1C). In addition, multivariate analysis demonstrated that PS and the presence of driver oncogene were significantly associated with prolonged OS (Table 3).

Therapeutic Outcomes

Next, we investigated the association between therapeutic interventions after the diagnosis of MPC and survival benefit. Twenty-five patients (54.3%) who received at least one line of anti-cancer treatment after MPC diagnosis were categorized as the treatment group, and the other 21 patients (45.7%) who were not administered any anti-cancer agent made up the best supportive care (BSC)

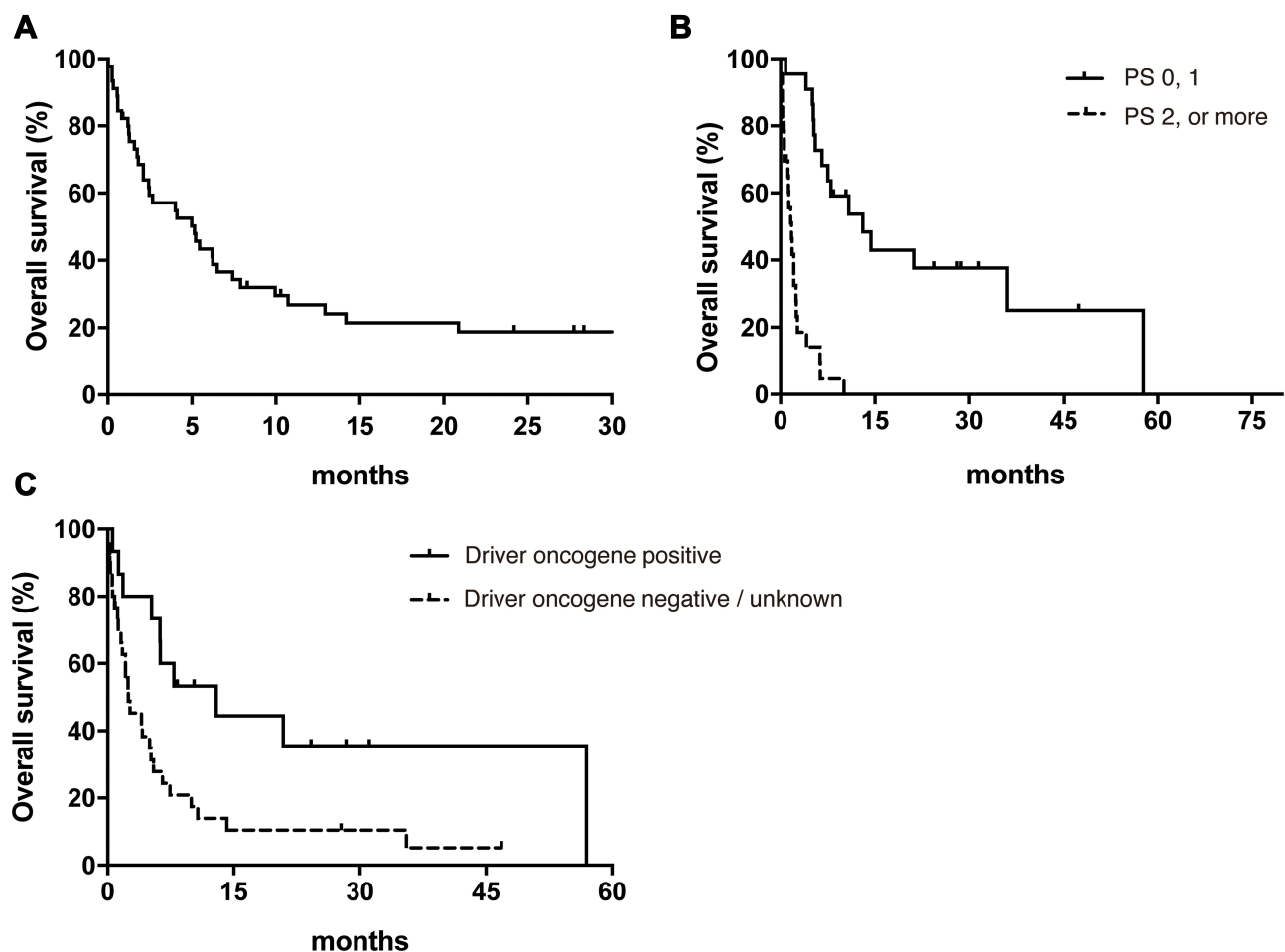


Figure 1 Kaplan–Meier analysis of overall survival in all patients (A), in the good and poor PS groups (B) and in the driver oncogene positive and negative or unknown groups (C).

Abbreviation: PS, performance status.

Table 2 The Univariate Analysis of Clinical Factors Associated with OS (Log Rank Test)

Item	Category	N	Hazard Ratio (95% CI)	P-value
Age (years)	< 75	35	Reference	
	≥75	11	1.33 (0.59–3.00)	<i>p</i> = 0.50
Sex	Male	33	Reference	
	Female	13	0.95 (0.47–1.93)	<i>p</i> = 0.90
Smoking history	Non-smoker	10	Reference	
	Smoker	36	1.57 (0.79–3.15)	<i>p</i> = 0.20
Driver oncogene	Negative/Unknown	31	Reference	
	Positive	15	0.41 (0.21–0.81)	<i>p</i> = 0.010
PS	0, I	22	Reference	
	2, 3, 4	24	11.2 (4.86–25.8)	<i>p</i> < 0.001
Onset of MPC	Initial	12	Reference	
	Late	34	1.24 (0.60–2.60)	<i>p</i> = 0.57
Malignant ascites	No	31	Reference	
	Yes	15	0.63 (0.32–1.22)	<i>p</i> = 0.17
Previous treatment history	No	14	Reference	
	Yes	32	0.75 (0.28–1.98)	<i>p</i> = 0.90
Abdominal symptom	No	24	Reference	
	Yes	22	1.19	<i>p</i> = 0.97
Brain metastasis	No	41	Reference	
	Yes	5	1.03 (0.68–1.39)	<i>p</i> = 0.89
Malignant pleural effusions	No	29	Reference	
	Yes	17	0.99 (0.51–1.93)	<i>P</i> = 0.97

group. The median OS in the treatment group (9.3 months, 95% CI 5.3–35.6 months) was significantly longer than that in the BSC group (1.3 months, 95% CI 0.33–2.4 months) (hazard ratio, 0.10; 95% CI, 0.042 to 0.25; *P*<0.0001) (Figure 2A). In the treatment group, cytotoxic

agents, EGFR/ALK-tyrosine kinase inhibitors (EGFR/ALK-TKI), and immune-checkpoint inhibitors (ICI) were administered for 13, 10, and 2 patients, respectively. Three patients received bevacizumab with a cytotoxic agent or EGFR-TKI. The median OS in the groups treated with cytotoxic agent and EGFR/ALK-TKI was 6.2 and 20.9 months, respectively (hazard ratio, 0.10; 95% CI, 0.042 to 0.25; *P*<0.0001) (Figure 2B). In the EGFR/ALK-TKI group, 6 were TKI-naïve patients and the other 4 had previously received retreatment with a TKI (Figure 2C). All TKI-naïve patients were continuously administered TKI for more than 7 months, whereas no one in the TKI-retreatment group continued TKI beyond 4 months due to the worsening of PS or the disease progression.

Discussion

Extrapulmonary metastasis in NSCLC is commonly observed and the optimal treatment strategies have been extensively investigated. In terms of MPC, especially in lung cancer patients, little is known about whether therapeutic interventions should be actively recommended and what type of treatment should be selected. Our retrospective multi-center study recruited 46 NSCLC patients with MPC, then clarified their clinical characteristics. We demonstrated that systemic drug therapy above and beyond BSC may result in prolonged survival in certain patient populations.

First, this study shows the profile of histological subtypes associated with MPC, predominantly adenocarcinoma. Besides, in patients with lung adenocarcinoma, MPE is common during treatment.⁹ Our results are in line with previous work by Su et al and Patil et al demonstrating that 25 of 30 lung cancer cases with MPC had adenocarcinoma⁸ and 26 of 33 non-squamous NSCLC patients with MPC had MPE,⁹ respectively.

Multivariate analysis revealed that the presence of a driver oncogene as well as better PS was associated with prolonged OS. A retrospective study investigating 60 NSCLC patients with MPC by Abbate et al had

Table 3 The Multivariate Analysis of Clinical Factors Associated with OS (Cox Proportional Hazards Model)

Item	Category	N	Hazard Ratio (95% CI)	P-value
Driver oncogene	Negative/Unknown	31	Reference	
	Positive	15	0.46 (0.21–0.99)	<i>p</i> = 0.049
PS	0, I	22	Reference	
	2, 3, 4	24	7.84 (3.40–18.07)	<i>p</i> < 0.001

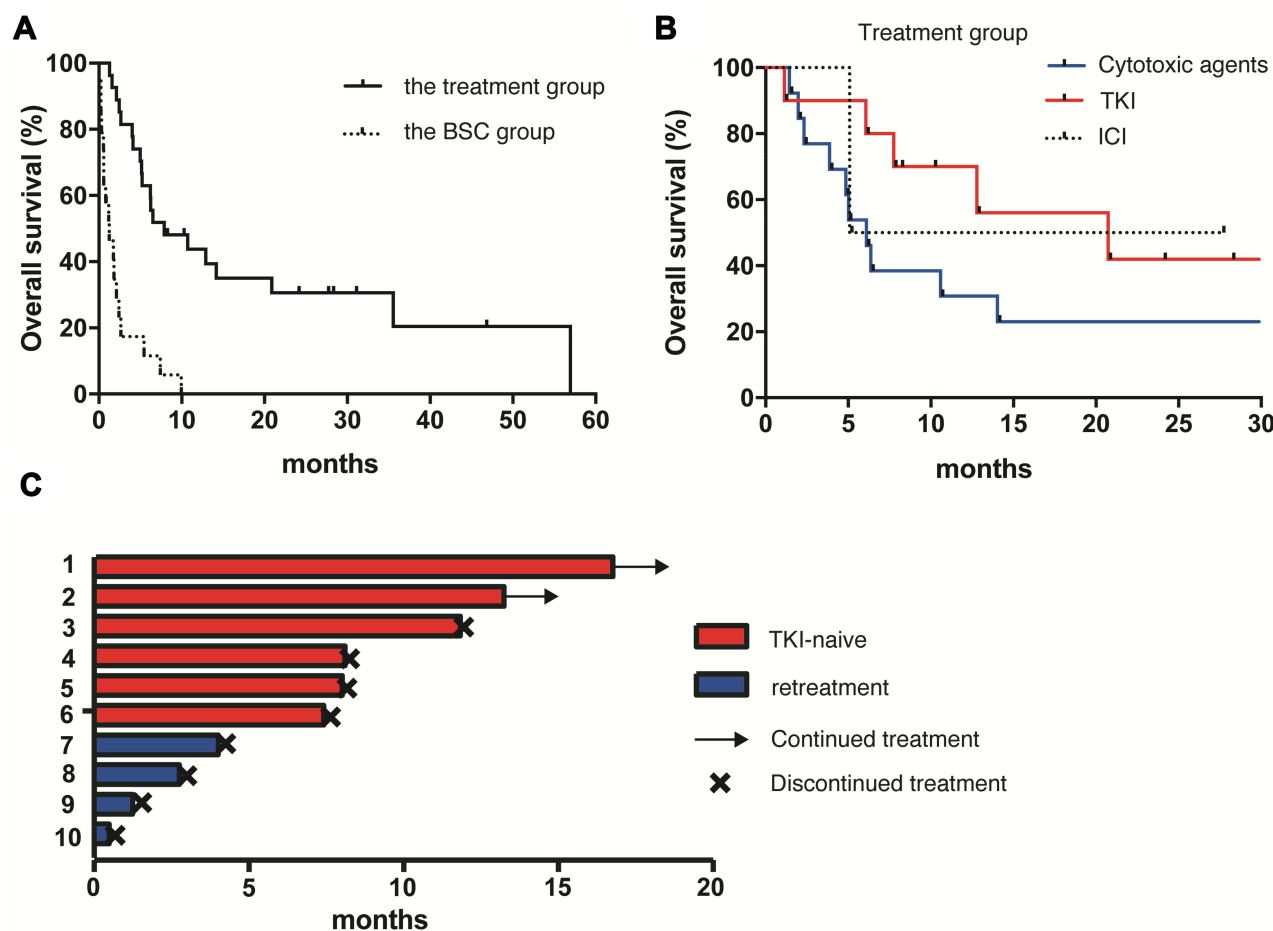


Figure 2 Kaplan–Meier analysis of overall survival in the treatment and the BSC groups (**A**), and in the groups treated with cytotoxic agents, TKI and ICI (**B**). Swimmer plot in the TKI-naïve and -retreatment groups (**C**).

Abbreviations: BSC, best supportive care; TKI, tyrosine kinase inhibitors; ICI, immune checkpoint inhibitors.

reported that overall survival in patients with EGFR mutations was better than in patients with wild type EGFR, likely as a result of receiving targeted agents more frequently.¹⁰ Our findings indicate that, in advanced lung cancer patients with MPC, histological subtype and genomic screening should be used to guide therapy. In this context, conducting ascites cytology with next-generation sequencing to detect genomic alterations may improve the prognosis of lung cancer patients with MPC.

Next, our study focused on how significantly therapeutic intervention affects prognosis. Median OS in the BSC group was less than 2 months and was as poor as that of NSCLC patients with symptomatic brain metastasis, considered one of the worst complications in advanced NSCLC.¹¹ Our findings agree with previous studies reporting median OS in lung cancer patients with MPC of only 15 days to 3.5 months.^{8,12} This is likely due to the high morbidity associated with MPC, which critically affects prognosis. In contrast, overall survival in patients receiving active treatment was significantly

improved when compared with that in the BSC group. Although peritoneal carcinomatosis from lung cancer may be one of the signs of the end of life, palliative systemic therapy should be considered since it appears to improve prognosis. The mechanisms underlying the efficacy of systemic anti-cancer therapy for MPC are not well understood. Here, drug penetrance and concentration in the peritoneal and pleural cavities are worth considering. Kobayashi et al reported that the concentration of paclitaxel intravenous administration reaches a sufficient concentration to suppress cancer cell growth in ascites of gastric cancer patients.¹³ This finding suggests that systemic cytotoxic agents may have the potential for anti-tumor activity by reaching the abdominal cavity. For small molecule inhibitors, there are several pharmacological studies investigating drug concentrations in pleural effusions, but no reports on concentrations in ascites.^{14,15} Since the median OS in the EGFR/ALK-TKI treatment group in our study was 20.9 months, comparable to previous studies investigating advanced lung cancer patients with metastasis, we

suppose that TKIs reach sufficient intraperitoneal concentrations to treat MPC.^{15,16} However, this clinical benefit was limited in TKI-retreated patients, who showed only transient response (Figure 2C). In order to avoid missing this promising treatment opportunity, genomic screening should always be considered in metastatic NSCLC.

There are some limitations to the current study. First, it is a retrospective study recruiting a limited number of patients with MPC. Second, the number of patients administered novel therapeutic agents such as bevacizumab and ICI is too small to objectively evaluate treatment efficacy. Programmed cell death ligand-1 (PD-L1) tumor proportion score (TPS) was examined in 7 patients (2%), then resulting in positive (TPS was at least 1% or more) for 5 patients. Nasserredine et al recently reported high prevalence of MPC patients with positive PD-L1 and showed limited number of responses to ICI treatment.¹⁷ Third, the prevalence of MPC in NSCLC with driver oncogene other than EGFR and ALK alteration has not yet been evaluated in our study, which is now commonly investigated using next-generation sequencing technology. Conducting a prospective study would prove challenging since NSCLC MPC is a rare complication that is difficult to predict in advance. A detailed and longitudinal observational study throughout the course of NSCLC treatment at a high-volume center would be helpful.

Conclusion

In retrospective analysis of 46 patients, we clarified clinical characteristics of MPC, a rare complication with NSCLC. Better PS and the presence of a driver oncogene were significantly associated with prolonged overall survival. Although the overall prognosis of MPC remains poor, palliative therapeutic interventions including cytotoxic agents and small molecule inhibitors may show a survival benefit even after the diagnosis of MPC.

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Disclosure

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