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Does the Amount of Malignant Pleural Effusion affect the Survival in Patients with Non-small Cell Lung Cancer?

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Abstract

Objective: Malignant pleural effusion (MPE) in patients with non-small cell lung cáncer (NSCLC) is uniformly classified as M1a/stage IV disease in the current TNM classification, irrespective of its amount, and it is considered to be an incurable disease condition. Although a small amount of MPE had been reported to be an early phase of pleural carcinomatosis, its clinical relevance has rarely been studied. In this study, we examined the influence of the amount of MPE on the survival of patients with NSCLC.

Materials and Methods: Sixty patients with pleural carcinomatosis referred to our institution between 2005 and 2012 were enrolled. The patients were classified into three groups according to the amount of MPE on chest computed tomography (CT): E0, no MPE (n=21); E1, a small amount of MPE (<1.0 cm thick on CT, n=19); and E2, a large amount of MPE (≥1.0 cm thick on CT, n=20). The association between the clinicopathological factors, including the amount of MPE, and the survival were investigated using univariate and multivariate analyses.

Results: The patients with E2 had significantly shorter survivals than the E0 and E1 groups (median survival of 16, 31, and 20 months, respectively; log-rank test, P<0.01), while there was no significant difference between the E0 and E1 groups. In the multivariate analysis, histology, EGFR gene mutation status, and the amount of MPE remained significant prognostic factors.

Conclusion: The amount of MPE in NSCLC might be an important prognostic factor and affect patient survival. In the TNM classification, the amount of MPE should be considered for inclusion in the definition of T descriptor or stage grouping.

Keywords Lung cancer; Pleural carcinomatosis; TNM classification; Pleural effusion

Introduction

Pleural carcinomatosis is defined as the progression of the primary cancer to the pleural cavity. Pleural carcinomatosis in non-small cell lung cancer (NSCLC) is detected as malignant pleural effusion (MPE) and/or pleural nodules. In general, patients with pleural carcinomatosis have extremely short survival and are treated without surgery, except for patients with MPE and/or nodules unexpectedly found during an operation [1,2]. The International Association for the Study of Lung Cancer (IASLC) staging project committee reported that patients with pleural carcinomatosis had a median overall survival of 8 months, with a 5-year survival of 2% using a large cohort [2]. Consequently, pleural carcinomatosis was uniformly classified as M1a/stage IV disease under the current TNM classification, irrespective of the amount of MPE. This status will appear in the forthcoming 8th edition of the TNM classification in 2016 [3]. Pleural carcinomatosis has been recognized in a variety of conditions, with various amounts of MPE and/or pleural nodules. Some patients show a large amount of effusion at their first visit to a hospital, while others show minimal MPE found intraoperatively. Several studies have evaluated the association between the amount of pleural effusion and patient prognosis [4,5] and the presence of pleural effusion has been identified as an independent indicator of a poor prognosis compared with no pleural effusion, although whether or not the effusion was carcinomatous was unclear. When pleural carcinomatosis is evaluated, only those patients with true pleural carcinomatosis should be included in the study. Therefore, we evaluated the association between the amount of MPE and the prognosis in patients with NSCLC from a retrospective cohort in a population consisting solely of patients with cytopathologically proven pleural carcinomatosis, regardless of their treatment history.

Materials and Methods

A cohort of 60 patients diagnosed with NSCLC with cytopathologically confirmed pleural carcinomatosis at Nagoya University Hospital between 2005 and 2012 was enrolled in this study. All of the information on prognostic variables was collected prospectively from the medical records. The study was approved by the

institutional review boards of Nagoya University Hospital. Themethods of the cytopathological diagnosis of pleural carcinomatosis were as follows: the intraoperative detection of MPE and/or pleural nodules in 27 patients, the confirmation of MPE through thoracentesis in 23 patients, and via CT-guided needle biopsy for pleural nodules in 10 patients. With regard to the treatment strategy for patients with pleural carcinomatosis we considered chemotherapy to be the standard, valid therapy. However, for young patients with a small amount of MPE and/or nodules unexpectedly found intraoperatively we performed lobectomy or elective extrapleural pneumonectomy, except for patients with a cN2 status.The variables were grouped as follows: patient-related variables of age, gender, and Eastern Cooperative Oncology Group performance status (ECOG PS); tumor-related variables of histology and epidermal growth factor receptor (EGFR) gene mutation status; and treatment-related variables of surgery with any treatment, chemotherapy, and best supportive care. Based on the amount of MPE on chest high- resolution computed tomography (HRCT) scans, the patients were classified into three groups: E0, no MPE (n=21); E1, a small amount of MPE (<1.0 cm thick on CT, n=19); and E2, a large amount of MPE (≥1.0 cm thick on CT, n=20) (Figure 1).

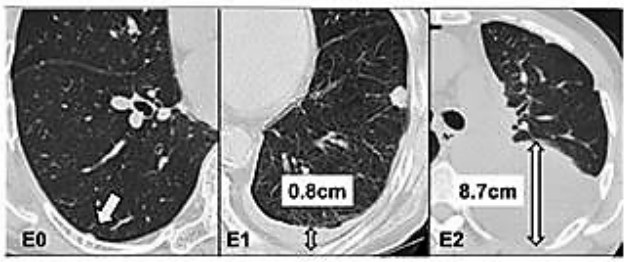


Figure 1: The patients were classified into three groups based on the amount of malignant pleural effusion (MPE) on chest high-resolution computed tomography scans, as follows: no MPE (E0,n=21), a small amount of MPE (<1.0 cm thick; E1, n=19; median thickness, 0.8 cm; range, 0.3-0.9 cm), and a large amount of MPE (≥1.0 cm thick; E2, n=20; median thickness, 10.8 cm; range, 1.2-20.6 cm).

The overall survival was measured as an outcome and estimated from the time of diagnosis until death from any cause or last follow-up. The association between the clinicopathological factors, including the amount of MPE, and the survival were investigated using univariate and multivariate Cox regression analyses. The survival curves for MPE statuses were estimated using the Kaplan-Meier method and these are compared by using the log-rank test. All significance testing was done at the two-sided $P<0.05$ level. All of the statistical analyses were performed using the SAS software package (version 9.3; SAS Institute Inc., Cary, NC, USA).

Results

The baseline patient's characteristics stratified by the MPE status are shown in Table 1. The median follow-up period of the patients was 21.0 months (0.5 to 106.0 months). 46 patients (76.7%) had adenocarcinoma histology. No marked differences in the six basic characteristics were noted among the E0 to E2 groups. Most of the patients underwent some chemotherapy (n=44, 81.7%). The regimens for first-line chemotherapy were as follows: 31 patients received cisplatin-based doublet, 8 patients received EGFR-tyrosine kinase inhibitors (TKI), and the others received single-agent chemotherapy. 9 patients underwent surgical treatment, as follows: extrapleural pneumonectomy with intent to cure was performed for three younger patients with cN0/1 nodal status, lobectomy and resection of pleural nodules were performed for 3 patients found to have pleural carcinomatosis intraoperatively, and lobectomy was performed in 3 patients who were diagnosed with pleural carcinomatosis after surgery 7 patients received the best supportive care, as follows: 2 patients refused chemotherapy, 3 patients had comorbidities such as idiopathic pneumonitis and low renal function, and 2 patients were elderly and had low performance status. 17 patients were positive for EGFR gene mutations, and 16 of them received EGFR-TKI at some point after the diagnosis of pleural carcinomatosis.

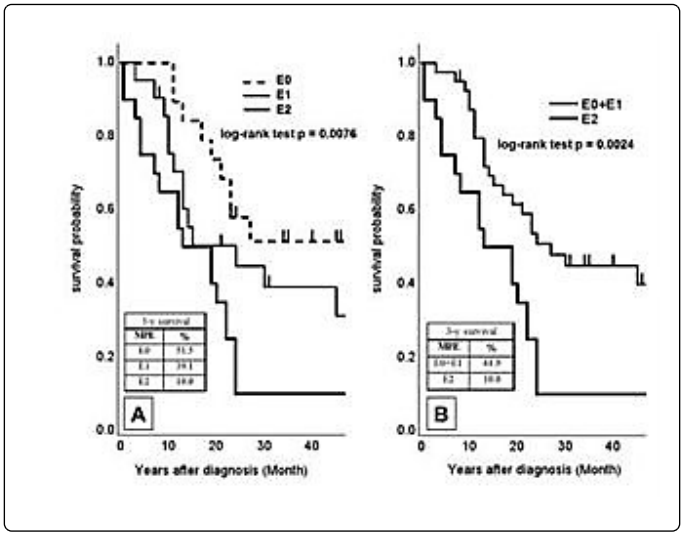
		Total (n=60)	E0 (n=21)	E1 (n=19)	E2 (n=20)
Median age	Years (range)	67	71	70	63
		(33-82)	(49-80)	(44-80)	(33-82)
Sex	Male	46	15	15	16
	Female	14	6	4	4
ECOG PS*2	0-1	55	21	17	17
	2	5	0	2	3
Histology	Adenocarcinoma	46	19	10	17
	Squamous Cell carcinoma	11	2	7	2
	Others	3	0	2	1
Initial treatment	Surgery	9	5	3	1
	Chemotherapy	44	14	15	15

	Best supportive care	7	1	2	4
EGFR*3 gene mutation	Positive	17	9	3	5
	Negative	24	7	7	10
	Unknown	19	5	9	5

*1MPE: Malignant Pleural Effusion, *2ECOG PS: Eastern Cooperative Oncology Group Performance Status, *3EGFR: Epidermal Growth Factor Receptor

Table 1: Baseline characteristics of patients according to the amount of MPE*1.

Although no significant differences were observed in the overall survival between the E0 and E1 groups (P=0.19), the patients in the E2 group showed significantly worse survival than those in the E0 and E1 groups (P<0.01) (Figure 2A). There was significant difference on overall survival between the E0+E1 and E2 groups (P<0.01) (Figure 2B).



		HR	**95% CI**	**P-value**
Sex	Male	1	0.14-0.82	0.2
	Female	33		
ECOG PS*1	0-1	1	2.42-17.99	<0.01
	2	6.6		
Histology	Adenocarcinoma	1	1.41-5.59	<0.01
	Others	2.81		
Initial treatment	Surgery	1	0.68-4.55	0.24
	Chemotherapy	1.76	2.06-24.86	<0.01
	Best supportive care	0.75		
EGFR*2 gene mutation	Positive	1	2.34-17.11	<0.01
	Negative	6.32		
Amount of MPE*3	E0+E1	1	1.38-4.72	<0.01
	E2	2.55		

*1ECOG PS: Eastern Cooperative Oncology Group Performance Status,*2EGFR: Epidermal Growth Factor Receptor, *3MPE: Malignant Pleural Effusion *1ECOG PS: Eastern Cooperative Oncology Group Performance Status,*2EGFR: Epidermal Growth Factor Receptor, *3MPE: Malignant Pleural Effusion

Table 2: Univariate analyses of prognostic factors by using cox proportional hazards model.

A univariate analysis using the Cox hazards model showed that male sex, ECOG PS2, non-adenocarcinoma histology, treatment with the best supportive care, a negative EGFR gene mutation status, and a large amount of MPE (E2 group) were significant factors for predicting poor overall survival (Table 2). Using a Cox proportional hazards model adjusted for all of the characteristics, non-adenocarcinoma histology, a negative EGFR gene mutation status, and a large amount of MPE (E2 group) were significant factors for predicting poor overall survival. The presence of a large amount of MPE was an independent prognostic factor of poor survival compared with the E0 + E1 group (adjusted HR, 2.51; 95% CI, 1.25 - 5.05; P<0.01) (Table 3).

		HR	**95% CI**	**P-value**
Sex	Male	1	0.21-1.61	0.29
	Female	0.58		
ECOG PS*1	0-1	1	0.61-36.60	0.14
	2	4.69		
Histology	Adenocarcinoma	1	1.31-8.54	0.01
	Others	3.35		
Initial treatment	Surgery	1	0.32-2.89	0.95

	Chemotherapy	0.97	0.09-6.67	0.8
	Best supportive care	0.76		
EGFR*2 gene mutation	Positive	1	1.96-16.15	<0.01
	Negative	5.63		
Amount of MPE*3	E0+E1	1	1.31-5.32	<0.01
	E2	2.64		
*1ECOG PS; Eastern Cooperative Oncology Group Performance Status, *2EGFR: Epidermal Growth Factor Receptor, *3MPE: alignant Pleural Effusion				

Table 3: Multivariate analyses of prognostic factors by using cox proportional hazards model.

Discussion

Lung cancer patients with pleural carcinomatosis are generally understood to have relatively poor survival [1,2]. However, long-term survivors have been reported sporadically [4-11]. Some investigators reported that those long-term survivors were eligible for surgical treatment. Recently, Iida et al. Documented the results of surgical intervention in NSCLC patients with pleural carcinomatosis from the Japanese Joint Committee of Lung Cancer Registry [11]. They assumed that pleural carcinomatosis was encountered at thoracotomy in patients whose effusion and/or pleural nodules were not definitively detected by preoperative examinations. The median survival time (MST) and 5-year survival of 313 patients without other metastatic disease were 34.0 months and 29.3%, respectively, and macroscopic complete resections were associated with better survival than incomplete resections. Thus, these authors found that certain patients with pleural carcinomatosis might be long-term survivors with surgery. Consequently, prognoses are now believed to be varied among NSCLC patients with pleural carcinomatosis.

Some studies have evaluated the association between the amount of pleural effusion and patient prognosis [10,11]. Initially, Sugiura et al. Investigated 197 patients with advanced NSCLC and evaluated whether or not the amount of pleural effusion had a prognostic impact10. They reported that pleural effusion in advanced NSCLC was an independent indicator of a poor prognosis compared with no pleural effusion (HR, 1.42; 95% CI, 1.00-1.98). Ryu et al. Conducted a similar study in 2,016 NSCLC patients [11]. They classified the patients into three groups based on their pleural effusion status: no pleural effusion, minimal pleural effusion, and malignant pleural effusion (MPE). Minimal pleural effusion correlated significantly with shorter survival compared with no pleural effusion (MST, 7.7 vs. 17.7 months; P<0.001). No significant difference was observed in the overall survival between patients with minimal pleural effusion and MPE. They hypothesized that patients with minimal pleural effusion might have had more severe comorbid diseases than those with no pleural effusion, which would have negatively influenced the survival. They also speculated that the severe comorbid diseases in the minimal effusion group might put them at equal risk of poor survival as the patients with MPE. However, in their report, it was unclear whether or not the minimal effusion was carcinomatous. When pleural carcinomatosis is evaluated, then only those patients with cytologically or pathologically proven carcinomatous pleuritis should be enrolled in the study.

For this reason, in the present study, we examined only patients with cytopathologically proven pleural carcinomatosis. The patients enrolled in our study were classified into three groups based on the amount of MPE on HRCT, as described in the previous report of Ryu et al. A large amount of MPE was found to be significantly correlated with a relatively short survival than a smaller amount of MPE. However, no significant differences were noted in survival between the E0 and E1 groups. A multivariate analysis showed that adenocarcinoma histology and positive EGFR mutation status were favorable prognostic factors in addition to the amount of MPE, findings which were not consistent with those of previous reports [12,13].

In the present study, the risk of death gradually increased with the increasing amount of MPE in patients with malignant carcinomatosis, from no effusion up to a large amount of MPE. An increased tumor burden within the pleural space has been suggested to be associated with worse survival among patients with MPE [14]. Given these present and previous findings, we hypothesized that a small amount of MPE was the early phase and a large amount of MPE the advanced phase of pleural carcinomatosis. In general, two different pathways have been advocated for this hypothesis. One pathway is via the direct or local extension of the tumor. After exfoliated cells seed the pleura, they drain into the subpleural lymphatic system through the preformed stomata, which results in lymph node metastasis or more distant metastasis by way of the systemic circulation [15]. This pathway seems to take match time up to the systemic or advanced stage. The second pathway is via blood stream dissemination and seems to resemble the systemic progression of cancer. Although we believe that large amounts of MPE are not produced in the early phases of pleural carcinomatosis, a substantial amount is produced in the systemic stage, and the patients tend to have poor prognoses. This study had several limitations, in which it was conducted by retrospective design and studied relatively small number of patients.

Conclusion

In the present study, patients with a small amount of MPE had a 3 year survival of 45% and relatively good survival, even in patients with M1a disease. This survival rate may be comparable to that of stage III patients in the 7th TNM classification. The amount of MPE in NSCLC might be an important prognostic factor and affect patient survival. Taken together, these findings indicate that the disease status and prognosis of patients with pleural carcinomatosis are not uniform. As such, the uniform classification of pleural carcinomatosis as M1a/stage IV disease in the TNM classification, irrespective of the amount of MPE, may be inappropriate. We will soon validate this observation in a prospective observational clinical study for NSCLC patients with pleural carcinomatosis.

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