

The role of surgical intervention in lung cancer with carcinomatous pleuritis

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Contributions: (I) Conception and design: All authors; (II) Administrative support: T Fukui; (III) Provision of study materials or patients: T Fukui; (IV) Collection and assembly of data: T Fukui; (V) Data analysis and interpretation: T Fukui; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Patients with non-small cell lung cancer (NSCLC) associated with carcinomatous pleuritis are currently classified as having stage IV disease per the 7th edition of the tumor-node-metastasis (TNM) system, which means that the disease is deemed incurable. In fact, the 5-year survival rate of these patients was only 2% in a large global cohort collected by the International Association for the Study of Lung Cancer. However, patients with carcinomatous pleuritis have heterogeneous conditions. Some have minimal pleural effusion, which is first detected at thoracotomy; some have numerous pleural nodules without any effusion; and others have massive effusion and nodules with symptoms. Several investigators have reported the contribution of surgical intervention to favorable outcomes of patients with carcinomatous pleuritis first detected at thoracotomy. These reports show a relatively higher 5-year survival rate of 15% to 37%. The extrapleural pneumonectomy (EPP) is a radical surgical procedure that is commonly employed in the treatment of malignant pleural mesothelioma. Two authors reported that they have successfully performed EPPs for the treatment of patients with carcinomatous pleuritis. Their 5-year survival rates were estimated to be 22% and 61%, a significantly improved outcome. Although the development of chemotherapeutic agents, including molecular targeted drugs, might have the potential to prolong the survival of patients with advanced lung cancer, surgical interventions including EPP might have a role in improving the survival of patients with carcinomatous pleuritis of minimal disease and those without massive effusion or numerous pleural nodules.

Keywords: Non-small cell lung cancer (NSCLC); carcinomatous pleuritic; extrapleural pneumonectomy (EPP); malignant pleural effusion (MPE); malignant pleural nodule (MPN)

Submitted Apr 29, 2016. Accepted for publication May 10, 2016.

doi: 10.21037/jtd.2016.06.36

View this article at: <http://dx.doi.org/10.21037/jtd.2016.06.36>

Introduction

Non-small cell lung cancer (NSCLC) associated with carcinomatous pleuritis, which includes malignant pleural effusion (MPE) and/or malignant pleural nodules (MPNs), is generally considered to be incurable, and in the latest 7th edition of the tumor-node-metastasis (TNM) classification these cases have been classified as stage IV disease (1). The International Association for the Study of Lung Cancer

(IASLC) reviewed the former TMN staging for lung cancer and recommended several revisions in 2007 (2,3). One of the most significant revisions was to classify carcinomatous pleural disease, either with MPE or MPNs without evidence of other metastatic disease, under the M1a category, making it stage IV disease. IASLC also reported the 1- and 5-year survival rates of patients with carcinomatous pleuritis were 36% and 2%, respectively, using their large globally collected cohort. This is a worse outcome than for other

Table 1 The population of patients with carcinomatous pleuritis first detected at thoracotomy

Author	Year	Period	No. of all patients	Carcinomatous pleuritis	
				No. of patients	%
Ichinose (4)	2000	1985–1994	8,813	284	3.2
Fukuse (5)	2001	1981–1997	1,086	49	4.5
Mordant (13)	2011	1983–2006	4,668	70	1.5
Okamoto (8)	2012	1990–2007	1,623	73	4.5
Iida (14)	2015	2004	11,420	232	2.0

T4M0 cases, but is better than that of patients with distant metastases, where the median survival is only 4 to 7 months.

NSCLC patients only found to have carcinomatous pleuritis at thoracotomy are also classified as having stage IV disease, even though they are expected to have minimal disease. In clinical practice, surgeons sometimes encounter such patients with ‘occult’ carcinomatous pleuritis; however, the standard treatment for such patients is not established in any clinical guidelines. Thus, various treatments such as the best supportive care, systemic chemotherapies using cytotoxic agents or molecular targeted drugs, or surgical interventions including extrapleural pneumonectomy (EPP), have been employed in Japan (4–11).

This review article is intended to provide an overview of our current understanding of carcinomatous pleuritis of NSCLC and to discuss the clinical implications of surgical interventions for patients with carcinomatous pleuritis.

Patients with carcinomatous pleuritis detected at thoracotomy

Patients with carcinomatous pleuritis are acknowledged to be very diverse; some have minimal amounts of MPE, which is first detected at thoracotomy; some have numerous MPNs without any effusion; and others have massive amounts of MPE and MPNs with symptoms. For patients with massive MPE and/or MPNs, which is apparent by radiological evaluation, systemic chemotherapy is the gold standard of treatment, the same as for other types of stage IV disease. However, the survival outcome of these patients is thought to be poor. In addition, whether MPE and MPN represent the same disease condition is unclear. Several studies have reported that there is no significant difference in survival outcomes between patients with MPE or MPN (4,8), but Fukuse *et al.* demonstrated that patients with MPE had a better prognosis than those with MPN (5).

The population of patients with carcinomatous pleuritis

first detected at thoracotomy ranges from 1.5% to 4.5% for all surgical cases (4,5,8,12,13) (*Table 1*). Ichinose *et al.* reported the first series of 284 patients (3.2%) found to have carcinomatous pleuritis at thoracotomy among 8,813 patients collected by the Japan Clinical Oncology Group (JCOG) (4). The Japanese Joint Committee of Lung Cancer Registry reported that among the 11,420 registered NSCLC patients who underwent surgical intervention in 2004, 329 patients had carcinomatous pleuritis (2.9%) (14). The population has not changed during the last decade.

Iida *et al.* reported an elevation of preoperative serum tumor markers, which include carcinoembryonic antigen, squamous cell carcinoma-related antigen, cytokeratin 19 fragment, Sialyl Lewis X, neuron-specific enolase, and progastrin-releasing peptide; nonsquamous cell carcinoma histology; larger tumor size; and lymph node involvement were significantly associated with a higher incidence of carcinomatous pleuritis (14).

Surgical intervention for carcinomatous pleuritis

The prognostic outcomes of patients with carcinomatous pleuritis have also been recognized to be variable, because of the heterogeneity in the extent of disease and the amount of effusion. Pulmonary resections, including partial resection, segmentectomy, lobectomy, and pneumonectomy, are generally contraindicated for patients with carcinomatous pleuritis. However, several investigators have reported that the postoperative prognosis of patients with carcinomatous pleuritis discovered at thoracotomy was relatively favorable (4,6,8,13,15) (*Table 2*).

Ichinose *et al.* reported the outcomes of 193 patients with carcinomatous pleuritis who underwent pulmonary resections, including 29 pneumonectomies, using the cohort of the JCOG described above (4). Among them, no gross residual tumor apart from the carcinomatous pleuritis remained in 155 (69%) patients. The 3- and

Table 2 Postoperative prognosis of patients with carcinomatous pleuritis

Author	Year	No. of patients	Procedure			Outcome	
			Segmentectomy/ partial resection	Lobectomy	Pneumonectomy [EPP]	MST	5-year survival rate (%)
Ichinose (4)	2000	193	25	139	29	17	14.9
Ichinose (6)	2001	100	10	79	11	21	22.8
Mordant (13)	2011	32	0	23	9	15	16.2
Okamoto (8)	2012	73	8	62	3	30	23.7
Iida (14)	2015	256	70	165	21	34*	29.3*
Yokoi (16)	2013	23	0	0	23 [23]	34	33.7
Yamaguchi (17)	2015	9	0	0	9 [9]	32	22.2

EPP, extrapleural pneumonectomy; MST, median survival time. *, including 57 patients with exploratory thoracotomy.

5-year survival rates of the 193 patients who underwent resection were 28.8% and 14.9%, respectively. They also analyzed the prognosis of 100 patients with minimal disease carcinomatous pleuritis. Minimal disease consisted of three conditions: no MPE and a small number of MPNs, MPE less than 300 mL and no MPNs, and MPE less than 300 mL and a small number of MPNs. The 3- and 5-year survival rates were 31.8% and 22.8%, respectively. The authors commented that the outcomes of resected NSCLC patients with minimal disease carcinomatous pleuritis were unexpectedly good.

Fukuse *et al.* evaluated 49 Japanese patients with lung cancer who were first diagnosed with MPE and/or MPN at thoracotomy (5). Partial resection was performed in seven patients, lobectomy in 27, and EPP in five. Radical dissection of the mediastinal and hilar lymph nodes was performed in the 32 patients who underwent lobectomy or EPP. The median survival times of the partial resection and lobectomy patients were 23.2 and 37.9 months, respectively.

In France, Mordant *et al.* investigated 32 patients with unexpected carcinomatous pleuritis at thoracotomy who underwent attempted curative pulmonary resection (13). A total of nine pneumonectomies and 23 lobectomies, along with mediastinal lymph node dissection and surgical resection of MPNs, were performed. The 5-year survival rate was 16% after resection, and 21% if the resection was a lobectomy.

Using the Japanese Joint Committee of Lung Cancer Registry, Iida *et al.* also reported the survival outcomes of patients with carcinomatous pleuritis (14). The median survival time and 5-year survival rate of 313 patients without other metastatic disease were 34.0 months and 29.3%, respectively. Primary tumor resection was performed in

256 (81.8%) patients, and macroscopic complete resection was achieved in 152 (48.6%) patients, with 5-year survival rates of 33.1% and 37.1%, respectively. The authors concluded achieving macroscopic complete resection was an independent prognostic factor.

Previous reports showed relatively higher 5-year survival rates of 15% to 37% for surgically treated cases while 5-year survival of all patients with M1a disease was estimated at 2% by the IASLC (2). Thus, surgical intervention, including major pulmonary resections, might contribute to better survival of patients with minimal disease carcinomatous pleuritis.

EPP for carcinomatous pleuritis

EPP is an en bloc resection of the lung along with the parietal and visceral pleurae and also usually the ipsilateral diaphragm and pericardium. EPP is commonly employed in the treatment of malignant pleural mesothelioma. A few authors have reported that they have successfully performed EPP in the context of treatment of MPE/MPN of non-mesothelioma malignancies, including NSCLC (15-17) (Table 2).

Yokoi *et al.* reported the prognostic outcomes of 23 NSCLC patients who underwent EPP between 1988 and 2012, with a median survival time and 5-year survival rate of 34 months and 34%, respectively (15,16). Among 12 patients with pathologic N0-1 disease, six remained alive without disease at 4 to 288 months after surgery, for a median survival time and 5-year survival rate of 126 months and 61%, respectively, a significantly better prognosis. The authors concluded that patients with N0-1 disease and carcinomatous pleuritis might be candidates for surgical

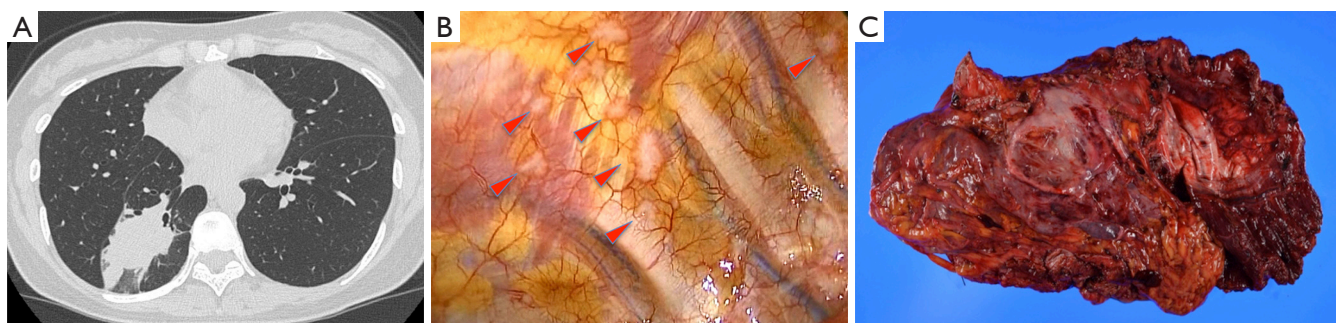


Figure 1 A representative patient of 43-year-old woman with lung cancer showing carcinomatous pleuritis who underwent induction systemic chemotherapy followed by extrapleural pneumonectomy. (A) Chest computed tomography of the patient shows a 6.7 cm × 3.6 cm mass in the right lung (S9) with pleural indentation; (B) thoracoscopic evaluation revealed numerous pleural nodules in the thoracic cavity without effusion (arrowheads); (C) an en bloc resection of the right lung along with the parietal and visceral pleurae and part of the ipsilateral diaphragm and pericardium.

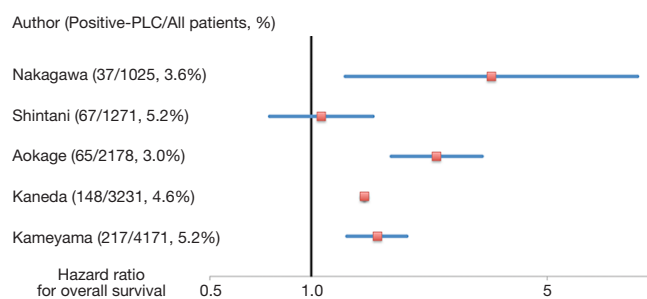


Figure 2 A forest plot evaluating the effect on overall survival of patients with positive pleural lavage cytology (PLC) results. Each error bar indicates the 95% confidence interval. Most reports suggest intraoperative positive PLC status is a significant prognostic factor indicating a worse outcome for patients with lung cancer.

treatment, including EPP.

Yamaguchi *et al.* evaluated the survival of 11 NSCLC patients who underwent induction chemoradiotherapy using uracil-tegafur (UFT[®], Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) plus cisplatin concurrently with 40 Gy hemithorax radiation followed by EPP from 1997 to 2004 (17). The 1-, 3- and 5-year overall survival rates were 100.0%, 33.3%, and 22.2%, respectively, with a median survival time of 32.1 months. The authors commented that induction therapy using UFT plus cisplatin with hemithorax radiation, followed by EPP, was feasible for NSCLC patients with carcinomatous pleuritis. However, the impact of this treatment on overall survival remains unclear.

However, a worse outcome after surgery has also been reported. Fukuse *et al.* performed EPP on five patients with carcinomatous pleuritis, and four of the five patients died

less than a year after surgery (5).

Here, we present a NSCLC patient with carcinomatous pleuritis who underwent induction systemic chemotherapy followed by EPP in our institution. A 43-year-old woman was scheduled to undergo pulmonary resection due to adenocarcinoma of the right lung. Chest computed tomography showed a 6.7 cm × 3.6 cm mass in the right lung (S9) with pleural indentation (*Figure 1A*). Because thoracoscopic evaluation revealed numerous MPNs in the thoracic cavity without MPE (*Figure 1B*), she was diagnosed with stage IV disease. Six cycles of systemic chemotherapy with cisplatin and pemetrexed was administered. After completion of chemotherapy, she underwent a right EPP with R0 resection (*Figure 1C*). She has been alive for 18 months without any recurrence.

Evaluation of the pleural lavage cytology

Pleural lavage cytology (PLC) is a diagnostic technique used to detect tumor cells in the pleural cavity and translate this finding to a prognostic index. PLC, which is performed at thoracotomy, is generally regarded to have a prophase of or latent carcinomatous pleuritis. In fact, many reports suggest a positive intraoperative PLC status is a prognostic factor indicating a worse outcome for patients with NSCLC (18-25) (*Figure 2*).

A meta-analysis performed by Saso *et al.* reported the association between positive PLC results and pleural, distant, and overall tumor recurrence in 4,450 patients undergoing surgical resection (20). Positive pre-resection PLC was associated with a higher rate of overall recurrence [odds ratio (OR): 4.82, 95% confidence interval (CI): 2.45 to 9.51],

pleural recurrence (OR: 9.89, 95% CI: 5.95 to 16.44), distant cancer recurrence (OR: 3.18, 95% CI: 1.57 to 6.46), and unfavorable patient survival outcomes [hazard ratio (HR): 2.08, 95% CI: 1.71 to 2.52] (20). The authors suggested postoperative adjuvant chemotherapy should be considered in the management of patients with positive PLC.

Kameyama *et al.* reported the clinical implications of PLC using the Japanese Joint Committee of Lung Cancer Registry (19). A total of 4,171 patients were enrolled and 217 patients (5.2%) had positive PLC results. The 5-year survival was 44.5% for patients with positive PLC results and 72.8% for patients with negative PLC results, which indicated a significantly worse prognosis for patients with positive PLC results. The authors suggested an upgrade of T stage in patients with positive PLC, because the significant survival differences between patients with positive and negative PLC results disappeared when the upstage was performed.

Although negative survival influences among patients with positive PLC have been reported, pulmonary resection in these patients should not be neglected because the results of PLC do not change the T stage classification of patients according to either the 7th or the upcoming 8th TNM classification (1,26,27).

Advances in systemic chemotherapy

Several drugs can be used to treat NSCLC, including traditional and targeted chemotherapeutic agents. Targeted cancer therapies are a new class of drugs that specifically target certain molecular pathways leading to cancer phenotypes. For example, it is well known that mutations of the epidermal growth factor receptor (*EGFR*) gene are specifically detected in lung adenocarcinoma, with the implication that patients with this genotype are super-responders to *EGFR* tyrosine kinase inhibitors, such as gefitinib and erlotinib (28-30). Another treatment option is the combination of the antimetabolite pemetrexed and the angiogenesis inhibitor bevacizumab, which has been approved for the initial treatment of advanced nonsquamous NSCLCs, a specific type of NSCLC (31-34). Recently, in patients with advanced squamous and nonsquamous-cell NSCLC, significantly better survival with nivolumab, a fully human IgG4 programmed death 1 immune-checkpoint-inhibitor antibody, as compared with docetaxel, was reported (35,36). The development of the agents described above might have the potential to prolong the survival of

NSCLC patients with advanced disease, including those with carcinomatous pleuritis. Consequently, the role of surgical intervention for these patients might change in the near future. However, we believe that surgical intervention has a role to play because the effect of these new drugs on survival is still unclear.

Conclusions

NSCLC patients with carcinomatous pleuritis show heterogeneous conditions. For the cases with minimal disease, which do not involve massive MPE or numerous MPNs, surgical interventions, including EPP, might have a role in improving survival. However, especially for EPP, we believe surgical intervention should be performed by experienced teams at experienced centers to minimize the morbidity and mortality associated with this radical procedure. In addition, if possible, additional prospective studies are needed to better characterize the role of surgical intervention in the multimodality treatment of patients with carcinomatous pleuritis.

Acknowledgements

None.

Footnote

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

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Cite this article as: Fukui T, Yokoi K. The role of surgical intervention in lung cancer with carcinomatous pleuritis. *J Thorac Dis* 2016;8(Suppl 11):S901-S907. doi: 10.21037/jtd.2016.06.36