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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Patient Survival after Surgical Management in Intrathoracic *Pseudomyxoma peritonei*

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ABSTRACT

Background. *Pseudomyxoma peritonei* (PMP) is a rare disease, characterized by mucinous ascites and deposits diffusely present on the peritoneal surfaces. However, extension of PMP to the thoracic cavity is extremely rare. Although there are a few case reports on the long-term postoperative prognosis of intrathoracic lesions, whether surgical resection of these lesions can improve patient prognosis remains unclear.

Methods. We reviewed 17 patients with PMP who underwent resection of intrathoracic lesions after abdominal cytoreductive surgery and examined their clinical outcome after surgery.

Results. Direct extension into the pleural cavity was identified in 11 patients. Extrapleural pneumonectomy of the lesions followed by hyperthermic intrathoracic chemotherapy (HITOC) was performed in four patients, parietal pleurectomy and visceral tumor resection followed by HITOC in four patients, resection of all disseminated pleural and visceral lesions followed by HITOC in one patient, resection of a single disseminated lesion in one patient, and composite resection of basal segment with the diaphragm in one patient. Pulmonary metastases were found in six patients. Partial resection was performed in four patients, segmentectomy in one patient, and lobectomy in one patient. We could perform macroscopic resection of the tumor in all the cases. The 5-year overall survival rate after thoracic surgery for the 17 patients was 46.1% and relapse-free survival was 34.9%.

Conclusions. Resection of intrathoracic lesions of PMP after abdominal cytoreductive surgery achieved 5 years survival in at least 46.1% of the patients. Aggressive tumor resection should be considered for patients with PMP extending to thoracic cavity.

Pseudomyxoma peritonei (PMP) is a rare disease that is caused by the dissemination of a mucin-producing tumor, characterized by the accumulation of a mucinous substance in the peritoneal cavity, thereby leading to mucinous ascites. Although the optimal treatment for PMP has not been adequately defined, aggressive cytoreductive surgery with intraperitoneal chemotherapy has demonstrated prolonged survival.[1] The efficacy of surgical intervention for PMP is of particular interest to surgical oncologists because of the possibility of long-term survival or even a complete cure following aggressive locoregional therapy for this disseminating tumor.

Extension of PMP into the thoracic cavity is extremely rare and carries a poor prognosis.[2] Thus far, there has not been enough evidence to recognize surgical intervention for intrathoracic PMP as the approved treatment given that there are few case reports on resection of intrathoracic lesions. Systemic palliative chemotherapy remains the usual treatment option, and surgery with or without hyperthermic intrathoracic chemotherapy (HITOC) is performed only in specialized centers.[3] It is not clear whether surgical resection of thoracic lesions of PMP improves prognosis. Therefore, in the present study, we evaluated the effectiveness of surgical intervention in patients with intrathoracic PMP on long-term prognosis, regardless of whether there was pleural dissemination or lung metastasis.

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METHODS

Institutional review board approval was obtained for this study (Approval Number: 2018-0704-10), and the requirement for patient consent was not fulfilled because of the retrospective nature of this study.

The present study was a retrospective analysis of 17 patients who were surgically treated for intrathoracic PMP at our hospital between January 2010 and June 2018. We enrolled only patients in whom the abdominal PMP was controlled by cytoreductive surgery and HIPEC. Patient data were registered based on medical, surgical, and pathology records. Patient characteristics were recorded and listed descriptively. In all of the patients, extension of PMP into the thoracic cavity was confirmed by computed tomography of the chest. All patients were followed-up for at most 5 years.

All patients reviewed had undergone thoracic cytoreductive surgery for resection of all visible intrathoracic lesions. When the lesions were confirmed as pulmonary metastases or lung invasion, we performed resection of the lesion with surrounding lung tissue. In patients with pleural dissemination, we combined surgical procedures to resect all visible tumors: extrapleural pneumonectomy, parietal pleurectomy, simple removal of the lesions, resection of diaphragm, or combined resection of tumor and lung. Following the resection of disseminated lesions, the patients were administered HITOC. Saline and anticancer therapy with either cisplatin 100 mg/body plus mitomycin 20 mg/body or mitomycin 20 mg/body alone at 42–43 °C was administered in the thoracic cavity. We positioned two intrathoracic drains (1 inflow and 1 outflow) and circulated the medications for approximately 1 h following the resection. The patients were followed up for a maximum of 69 months to record outcomes of death or major postoperative complications.

Statistical analysis was performed using SPSS statistical software (version 22, SPSS, Inc., Chicago, IL). The Kaplan–Meier method was used to determine overall survival and relapse-free survival time from the time of surgery for intrathoracic PMP.

RESULTS

Patient Presentation

During the study period, 17 patients underwent resection for intrathoracic PMP in our hospital. The mean age at thoracic surgery was 52.3 (range 34–76) years. There were ten male patients and seven female patients. Fifteen patients were classified as having low-grade PMP, and two patients were classified as high-grade PMP. Their demographics have been summarized in Table 1. The mean period between abdominal cytoreductive surgery, and thoracic surgery was 48.4 (range 13–122) months. The mean follow-up after thoracic surgery was 25 (range 1–69) months.

Before intrathoracic surgery, seven patients (4 dissemination cases, 1 direct invasion case, and 2 pulmonary metastasis cases) received systemic chemotherapy. After intrathoracic surgery, all patients terminated their systemic chemotherapy.

Surgical Outcome

All patients underwent either thoracic cytoreductive surgery just before HITOC for disseminated disease or lung resection for pulmonary metastases. Of the patients with disseminated disease, four patients (24%) underwent extrapleural pneumonectomy plus HITOC, four patients (24%) underwent parietal pleurectomy and lung resection plus HITOC, one patient (5.9%) underwent simple removal of all the disseminated lesions plus HITOC, and one patient (5.9%) underwent resection of the single disseminated lesion. One patient had direct invasion into the lung through the diaphragm and underwent combined resection of the basal segment with diaphragm. In cases of metastases, four patients (24%) underwent partial resection of lung, one patient (5.9%) underwent segmentectomy, and one patient (5.9%) underwent lobectomy (Table 2). Hospital mortality rate was 5.9% (1 patient died from empyema after extrapleural pneumonectomy). Morbidity rate was 29% (5 patients). Empyema occurred in three patients (18%), duodenal ulcer in one patient (6%), and loss of appetite in one patient (6%) who needed total parenteral nutrition (Table 3). The 5-year overall survival rate after thoracic surgery was 46.1%, and relapse-free survival was 34.9% (Fig. 1). Median survival time was 45.5 months.

DISCUSSION

The purpose of this study was to determine whether surgery in cases of intrathoracic PMP contributed to prolonged survival. It has been reported that PMP has an annual incidence of two per million individuals; the majority were secondary to mucinous adenocarcinoma of the appendix.[2] PMP has been divided into low grade and high grade, with abdominal PMP having a 5-year overall survival rate of 63% for low-grade and 23% for high-grade disease, following surgical resection. The median survival rates were 7.7 years and 2.8 years for low-grade and high-grade disease, respectively.[4] PMP had been regarded as an incurable disease for a long time and is usually fatal if

TABLE 1 Patient characteristics

Characteristics	Number of patients $n = 17$	%
Age (years)	52.3 (34–76)	–
Sex		
Male	10	59
Female	7	41
Side of intrathoracic disease		
Right	11	65
Left	6	35
Patterns of extension in thoracic cavity		
Direct extension for pleural cavity	11	65
Pulmonary metastasis	6	35
Grade		
High	2	12
Low	15	88
Systemic chemotherapy before surgery		
Yes	7	41
No	10	59
Disease free interval (months)	48.4	–
(From first abdominal surgery to thoracic surgery)	(13 ~ 122)	

TABLE 2 Operative procedures for intrathoracic PMP

Location of intrathoracic cavity	Surgical procedures for intrathoracic PMP	N
Direct extension for pleural cavity		
Dissemination (multiple)	Extrapleural pneumonectomy + HITOC	4
	Parietal pleurectomy + lung resection + HITOC	4
	Removal of all disseminated lesions + HITOC	1
Dissemination (single)	Resection of disseminated lesion	1
Direct invasion to lung through diaphragm	Segmentectomy + partial resection of diaphragm	1
Pulmonary metastasis		
	Partial resection	4
	Segmentectomy	1
	Lobectomy	1

PMP pseudomyxoma peritonei, *HITOC* hyperthermic intrathoracic chemotherapy

TABLE 3 Postoperative complications

Complications	Type of extension	Surgical procedures	N	%
Empyema			3	18
1 Patient: bronchopleural fistula	Pulmonary metastasis	Lobectomy		
1 Patient: gastrointestinal-pleural fistula	Direct invasion to lung	Basal segmentectomy		
1 Patient: gastrointestinal-pleural fistula	Dissemination	Extrapleural pneumonectomy + HITOC		
Loss of appetite (need total parenteral nutrition)	Dissemination	Extrapleural pneumonectomy + HITOC	1	6
Duodenal ulcer	Dissemination	Parietal pleurectomy + lung resection + HITOC	1	6

HITOC hyperthermic intrathoracic chemotherapy

untreated. Repeated debulking surgeries were previously generally accepted as the treatment of choice. Some reports have showed that cytoreductive surgery, involving the resection of all visible peritoneal lesions, and HIPEC provided the possibility of a cure or a longer survival time than that with conventional treatments.[5] However, this

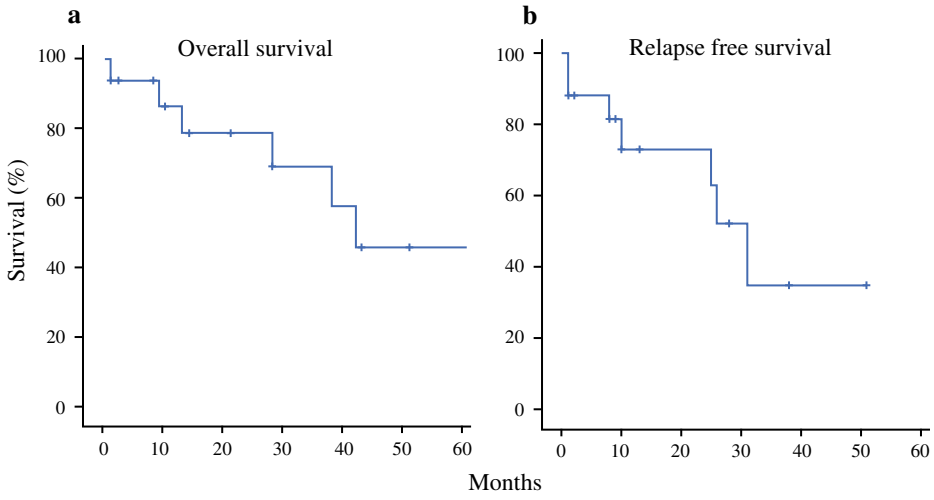

FIG. 1 Kaplan–Meier curves for overall survival (**a**) and relapse-free survival (**b**) of 17 patients with intrathoracic PMP after thoracic surgery, PMP, *pseudomyxoma peritonei*

aggressive locoregional cancer therapy is only performed at a limited number of specialized centers and is still the subject of controversy at the majority of institutions. In addition, the rare incidence of PMP, the complexity of the surgical procedures, and the high morbidity and mortality associated with the treatment are the main reasons that prevent it from being accepted as a standard surgical procedure in general.

Extension of PMP to the thoracic cavity is extremely rare. Pestieu et al.[2] have demonstrated that of 426 patients with abdominal PMP, 23 (5.4%) developed a pleural extension through the diaphragm, so-called mucus-mediated extension. Several mechanisms for explaining the invasion of tumor cells from the peritoneal cavity to the pleural space have been proposed, such as iatrogenic damage of the diaphragm during peritonectomy, the presence of congenital or acquired pleuroperitoneal communication, or direct invasion to diaphragm. The mechanisms are seldom described. Pestieau et al.2 have reported that, in their retrospective study of 426 patients with PMP, 52% of patients had pleural extensions resulting from minor penetration during diaphragmatic resection. Unlike most cancers, this disease rarely spreads through the lymphatic system or through the blood stream. A recent retrospective study has shown that of 626 cases of PMP, 42 (6.7%) cases of intrathoracic metastases were identified, which included 10 cases of pleural metastases, 22 cases of lung metastases, and 10 cases of both.[6]

Most patients with intrathoracic lesions are recommended only palliative care, because the treatments are associated with high morbidity and mortality, and intrathoracic extension carries a poor prognosis.[2,7] Lack of studies has been a major challenge in the management of this extremely rare condition. It is essential to establish long-term survival by early recommendation of treatment for intrathoracic PMP. There are a few case reports on operative management for intrathoracic lesions following abdominal cytoreductive surgery (Table 4).[2,3,8–11] In the six reports, six patients had pulmonary metastasis and ten patients had intrathoracic dissemination by mucus-mediated extension. They had undergone lung resection for metastatic lesions and intrathoracic cytoreductive surgery with or without HITOC for dissemination. Among them, one patient had achieved long-term survival of 8 years with no evidence of metastasis. We could find one report of nonoperative management cases in which bilateral dissemination treated by HITOC, but the patient died 6 months after treatment.[12]

In our study, we performed thoracic cytoreductive surgery following HITOC for dissemination or lung resection for pulmonary metastases. As a result, the 5-year overall survival rate after thoracic surgery was 46.1%, relapse-free survival was 34.9%, and median survival time was 45.5 months. From the time of abdominal cytoreductive surgery, we achieved a long-term survival of 93.9 months in this study. This result was longer than that of a previous large-scale study on surgical outcome for abdominal PMP, where the median survival time was 92 months for patients with low-grade PMP and 34 months for those with high-grade.[4] At present, intrathoracic cytoreductive surgery following HITOC for pleural dissemination and lung resection for pulmonary metastasis are recommended for long-term survival.

Patients who receive surgery for intrathoracic PMP require careful and intensive observation after surgery. Our data showed a high morbidity rate of 29%. Chronically, a poor nutritional status after abdominal resection might be a high-risk factor for surgery, especially in highly invasive thoracic surgery. In our study, only one patient with pulmonary metastasis developed complications. However, among those with dissemination or direct invasion of the thoracic cavity, four patients developed complications and

TABLE 4 Previous case reports on treatments for intrathoracic PMP

Report	Number of cases	Patterns of extension	Treatments	Present status	Follow-up period
Mortman et al.[8]	3	PM	2: Lobectomy 1: Wedge resection	No evidence of disease no Evidence of disease	2 years 8 years
Geisinger et al.[9]	2	PM	1: Lung resection 1: Wedge resection	No evidence of disease Not described	2 years not described
Kitai[10]	**1**	PM	Wedge resection	Died with disease	1 year
Pestieau et al.[2]	8	Dis	CRS + HITOC	5: No evidence of disease 2: Arrive with disease 1: Died with disease	2–42 months Not described Not described
Senthil et al.[11]	1	Dis	CRS + HITOC	No evidence of disease	6 months
Ababneh et al.[3]	1	Dis	CRS + HITOC	Arrive with disease	11 months

PM pulmonary metasis, *Dis* dissemination, *CRS* cytoreductive surgery, *HITOC* hyperthermic intrathoracic chemotherapy

one patient died of empyema. Hence, we need careful selection of cases for the surgical procedure as well as intensive postoperative management.

The main limitation of this study is its retrospective nature. The final decision to select a patient for surgery, the choice of surgical procedures, and regimens of HITOC may vary among surgeons. Some patients with potentially high morbidity and mortality risks or wide extent of disease, especially diaphragm might have been excluded beforehand, and they might receive just palliative treatment. Therefore, our study does not reflect the entire population of patients with intrathoracic PMP. A second limitation is the difficulty in interpretation of survival in our study. There are no data on a control group with intrathoracic PMP who did not receive surgery; therefore, we cannot conclude that our surgery definitely prolongs survival time. Furthermore, only two patients had high-grade PMP in our study. This might reflect on the overall survival of all patients, making it longer. A final limitation is the small number of cases in our study. To achieve more precise results, a prospectively designed, large comparative trial is required.

CONCLUSIONS

This study was the first report on the survival outcome of surgery for intrathoracic PMP. Long-term patient survival may be expected in cases where the abdominal lesions are controlled by cytoreductive surgery and HIPEC, and intrathoracic cytoreductive surgery following HITOC for intrathoracic lesions or resection of pulmonary metastasis is performed. However, to achieve more precise results, a prospectively designed, randomized-controlled trial is required.

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