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Local recurrence of tumor at sites of intervention in malignant pleural mesothelioma

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Summary In malignant pleural mesothelioma (MPM) patients, local dissemination (LD) of the tumor is frequently observed at the sites of intervention where diagnosis/treatment are performed. We evaluate the factors affecting LD frequency and discuss the use of PR in MPM patients.

Histopathologically diagnosed 212 MPM patients who had not received PR were evaulated in terms of development of LD. Of the 212 patients, 29 received supportive therapy, 157 received chemotherapy and 26 received multi-modal therapy. The LD frequency was 13.2% for all patients. The median survival rate was 9 or 10 months in patients with or without LD, respectively. A higher LD frequency was observed in patients receiving thoracotomy. The LD appearance time in supportive care is short. The LD frequency in patients treated with chemotherapy that revealed progressive disease was higher than the patients who revealed stable disease or objective response. LD developed in 2 months in patients with sarcomatous and mixed cell type, and the survival rate was low. LD was not associated with the stage of the disease. The most suitable candidate groups for PR are patients receiving supportive therapy, thoracotomy without multi-modal therapy or patients with sarcomatous and mixed cell type tumors.

1. Introduction

Malignant pleural mesothelioma (MPM) is a worldwide disease that will result in more than 250,000 deaths throughout the world within the next few decades [1]. Since this disease

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is almost invariably fatal, it poses an important health problem. Studies on the diagnosis and treatment modalities of MPM are therefore important and urgent.

Local dissemination (LD) of the tumor is a frequently seen complication that occurs at sites on the chest wall where invasive procedures such as needle biopsy, thoracoscopy and tube thoracotomy are performed in order to diagnose/treat MPM. Some authors concluded that LD necessitates preventive radiotherapy (PR) at the site of intervention [2—4]. In a randomized study, it has been shown that LD developed in 40% of patients who did not receive PR, whereas progression of LD was not observed in patients who received PR [2]. Local PR is commonly applied to MPM patients: this process is presented as group A evidence [2,4—6].

In recent years, multi-modal treatment and chemotherapy have been more commonly used to treat MPM patients [7]. The objective tumor response to regimes utilized for chemotherapy is around 30%. The use of some chemotherapy agents may prolong the lifespan of patients, or multi-modal treatment schedules prolong survival of the patients with early stage epithelial tumors [8—10]. Thus, the possibility of LD developing in the chest wall of patients receiving either chemotherapy with new regimes or receiving chemotherapy as part of a multi-modal treatment with complete hemithorax radiotherapy should be evaluated. Although prophylactic radiotherapy is absolutely recommended by certain guidelines in order to prevent LD [4,6], sufficient data concerning whether the stage of tumor, histopathological type, invasive procedure type, and treatment options affect the frequency of LD is not available. Furthermore, it is unclear whether the time of appearance of the LD and the role of LD itself affects the prognosis.

The aim of this study was to determine the LD rate and factors that affect the LD frequency in MPM patients who did not receive PR. In addition, we also examined whether patients had specific characteristics that could be used as indicators for PR. As the number of subjects used in this study is fairly large, the results should contribute towards clinical applications.

2. Methods and materials

The 231 consecutive patients who had definite histopathological diagnosis of MPM and who did not receive prophylactic radiotherapy on intervention sites of thorax in our clinic between January 1990 and April 2005 were included in the study. However, because a 12-month observation period is necessary for satisfactory assessment, the data of 212 MPM patients confirming the below-mentioned criteria of inclusion to the study were evaluated.

The eligibility criteria for all study participants are as follows: (1) patients who were treated with chemotherapy, and represent the response that has previously been assessed the least. These patients may have had a surgical procedure before chemotherapy for diagnosis and treatment purposes, but did not receive a multi-modal treatment. (2) Patients who received a good level of support treatment. (3) Patients who only received surgical treatment for diagnosis and palliative purposes. (4) Patients who were treated with multi-modal treatment that included a combination of surgery, chemotherapy and radiotherapy.

The male/female ratio, cell types, mean ages of the patients were determined. Patients were classified depending on the following criteria: type and time of treatment, invasive procedures utilized in the diagnosis, stage of the disease, the LD rate of the tumor, and the time of appearance of LD were determined and compared within the groups. The average life expectancy of the patients was established depending on whether the patients developed LD.

2.1. Chemotherapy protocol

Regarding adjuvant or therapeutic chemotherapy protocols used in our clinic, a combination of cisplatin, mitomycin C and recombinant interferon alpha 2a was used as the first protocol between 1990 and 1996. A combination of cisplatin, mitomycin C and ifosfamide was used as the second protocol between 1996 and 2000. A combination of cisplatin and gemcitabine (CG) was used as the third protocol between 2000 and 2005, and a combination of cisplatin and pemetrexed was used as the forth protocol after January 2005.

In the first protocol, cisplatin was given 30 mg/(m^2 day^{-1}) intravenously (iv) on days 1—2, mitomycin C 8 mg/m^2 iv on day 1 and intereferon alpha-2a 4.5 million IU subcutanously twice weekly. In the second protocol, cisplatin was given 75 mg/m^2 on day 1 iv, mitomycin C 8 mg/m^2 iv on day 1 and ifosfamide 2 g/m^2 iv on day 1. In the third protocol, cisplatin was given 75 mg/(m^2 day^{-1}) iv on day 1, gemcitabine 1250 mg/m^2 iv on days 1, 8. In the forth protocol, cisplatin was given 75 mg/m^2 on day 1 iv, pemeterexed 500 mg/m^2 iv on day 1. Chemotherapy cycles were repeated every 21 days.

2.2. Hemithoracic irradiation protocol

Adjuvant radiotherapy was delivered using photons by a dual energy (6- and 18-mv) linear accelerator. A minimum total dose of photons fields of 54 Gy (1.8 Gy/fraction, 1 fraction/day, 5 days/week) was delivered to the hemithorax, the thoracotomy incision and sites of chest drains. A boost dose of 9 Gy was considered for patients who had residual disease marked by surgical clips with photon fields. The radiotherapy planning ensures the coverage of the entire ipsilateral thoracic cavity from the apex to the diaphragm, ipsilateral mediastinum and surgical incisions and all scars. The treatment technique consisted of two opposed fields with custom blocks for each field, AP-PA, to the whole hemithorax, shielding organs at risk. The organs at risk were defined as spinal cord, kidneys, liver (for right-sided tumors). All of the treatment plans were done with CT-based planning system with adequate dose volume distribution for the target volumes and organs at risk.

2.3. Statistical analysis

All analyses were performed using statistical software (SPSS, version 11.5). Patients' characteristics according to gender were compared using the Pearson χ^2 test. Duration of survival and median and mean event times, with 95% confidence interval (CI), were estimated according to the Kaplan—Meier

Table 1 Patient characteristics

Patient characteristics	*n*
Number	212
Median survival time (year) (range)	57.9 ± 11.6 (26–97)
Male/female	120/92, 1.30
Cell type	
Epithelial	130 (61.3%)
Mixed	31 (14.6%)
Sarcomatous	21 (9.9%)
Undefined	30 (17.0%)
Stage	
I	42 (19.8%)
II	43 (20.3%)
III	91 (42.9%)
IV	36 (17.0%)
Method of diagnosis	
CPNB or CT-CPNB	135 (63.7%)
Thoracoscopy	46 (21.7%)
Thoracotomy	31 (14.6%)
Treatment type	
Supportive care	29 (13.7%)
Chemotherapy	157 (74.0%)
Multi-modal treatment	26 (12.3%)
Number of patients with local dissemination	28/212, 13.2%
Median survival time for all patients (months)	10 (95% CI: 9.1–10.9)
Appearance time for local dissemination median (month)	6 (95% CI; 4.9–7.0)

CPNB: closed pleural needle biopsy, CT-CPNB: computed tomography guided CPNB.

method. Differences in time distributions between groups were tested for statistical significance using the log-rank test. The significance level was considered to be 5% ($p = 0.05$) and the approach used was two-sided test.

3. Results

The clinical properties of all the histopathologically diagnosed MPM patients assessed during this study are shown in Table 1. Of the 212 patients, 120 were men and 92 were women. The mean age of the patients was 57.9 ± 11.6 years.

Table 2 The effects of gender on local dissemination rates

Gender	Local dissemination		*p*
	n	%	
Male	13/120	10.8	0.244
Female	15/92	16.3	

Table 2 shows that there was a higher occurrence of LD in women (16.3%) than men (10.8%), but not statistically significant ($p = 0.244$).

As shown in Table 3, we evaluated the frequency and appearance time of LD in patients who had been diagnosed by different methods. Either closed pleural needle biopsy (CPNB) or computed tomography guided CPNB (CT-CPNB) with thoracotomy or thoracoscopy was used during diagnosis. LD occurred more frequently in the thoracotomy patients (thoracotomy: 8/31 (25.8%) versus thoracoscopy and CPNB/CT-CPNB CT: 20/181 (11.0%: ($\chi^2 = 5.028$; $p = 0.025$). There was no difference between the median LD times and median survival times in terms of diagnostic procedures.

The LD frequency and median LD appearance times in terms of cell types are shown in Table 4, together with the median survival rate of the patients. Comparison of the LD frequency in patients with sarcomatous cell type is to patients with epithelial and mixed cell type tumors revealed a significant numerical difference that was not statistically significant (23.8% versus 11%: $\chi^2 = 2.684$; $p = 0.101$). The median LD appearance time in patients with sarcomatous and mixed cell types was shorter than in patients with epithelial cell type tumors, but this was not statistically significant (7 months versus 2 months: $\chi^2 = 3.190$; $p = 0.089$). Patients with epithelial-type MPM had a longer survival time than patients with mixed and sarcomatous-type MPM.

The LD frequency and median life expectancies in terms of the disease stage are shown in Table 5. The LD frequency was not associated with the stage of the disease. We show that the survival rate for stage 1 patients was significantly longer than for other stages.

The effect of different types of treatment on LD frequency, LD appearance times and survival times are shown in Table 6. The LD frequency in patients who received multi-modal treatment was twice as high as in patients who were treated with chemotherapy and than supportive care, although this difference was not statistically significant (23.1% versus 11.8%: $\chi^2 = 2.518$; $p = 0.113$). The LD appearance time in supportive care is quite short, this time is 12

Table 3 The effects of the diagnostic method used on local dissemination rates and appearance times

Diagnostic method	*n*	Local dissemination*		Median local dissemination time (month)** (95% CI)	Median survival (month)*** (95% CI)
		n	%		
CT ± CPNB	135	14	10.4	6 (4.2–7.8)	9 (7.9–10.1)
Thoracoscopy	46	6	13.0	6 (1.5–10.5)	11 (9.6–12.4)
Thoracotomy	31	8	25.8	5 (0.0–10.5)	10 (8.5–11.5)

*$p = 0.073$, **log-rank = 0.41; $p = 0.8155$, ***log-rank = 2.59; $p = 0.2733$.

Table 4 The effects of the cell type of the tumor on local dissemination rates and appearance times and the life expectancies of the patients

Cell type	*n*	Local dissemination*		Median local dissemination time (month)** (95% CI)	Median survival (month)*** (95% CI)
		n	%		
Epithelial	130	14	10.8	7 (5.2—8.8)	11 (9.4—12.6)
Mixed	31	4	12.9	2	8 (5.8—10.2)
Sarcomatous	21	5	23.8	2 (0.9—3.1)	7 (5.5—8.5)
Undefined	30	5	16.7	5 (0.7—9.3)	9 (7.6—10.4)

*$p = 0.384$, **log-rank: 3.12; $p = 0.3729$, ***log-rank: 16.36; $p = 0.010$.

Table 5 The effects of the disease stage on the local dissemination rates and median survival times

Cell type	*n*	Local dissemination*		Median survival time** (95% CI)
		n	%	
Stage 1	42	7	16.7	15 (11.0—18.9)
Stage 2	43	6	14.0	9 (5.4—12.6)
Stage 3	91	12	13.2	8 (6.6—9.4)
Stage 4	36	3	8.3	9 (7.6—10.4)

*$p = 0.752$, **log-rank: 15.12; $p = 0.0017$.

Table 6 The effects of the treatment types on the local dissemination rates, appearance times, and survival times of the patients

Treatment type	*n*	Local dissemination*		Median local dissemination time **(month) (95% CI)	Median survival time*** (month) (95% CI)
		n	%		
Supportive care	29	3	10.3	2 (0.4—3.6)	8 (5.9—10.1)
Chemotherapy	157	19	12.1	6 (5.2—6.8)	10 (8.9—11.1)
Multi-modal treatment	26	6	23.1	12 (0—25.7)	16 (8.2—23.9)

*$p = 0.275$, **log-rank = 8.0; $p = 0.0183$, ***log-rank = 12.47; $p = 0.002$.

months in patients who have been treated with multi-modal treatment. The median survival time in patients with multi-modal treatment was significantly longer than in patients treated by other methods.

The frequency of LD according to chemotherapy response, LD appearance times and survival times are shown in Table 7. Although the difference was not statistically significant, the LD frequency in patients who revealed progressive disease was twice as high as in patients who revealed stable disease and was more than threefold as high as in patients who revealed objective response. The LD appearance time in progressive disease group is 5 months, survival time is just 6 months.

As shown in Table 8 and Fig. 1, the median survival times in patients with or without LD were not significantly different.

Table 7 The effects of the chemotherapy response on the local dissemination rates, appearance times, and survival times of the patients

Response	*n*	Local dissemination *		Median local dissemination time **(month) (95% CI)	Median survival time*** (month) (95% CI)
		n	%		
Objective response	41	2	4.9	17 (0.0—80.6)	13 (9.4—16.7)
Stable disease	50	5	10	7 (6.1—7.9)	13 (10.3—15.7)
Progressive disease	67	12	18.2	5 (1.7—8.4)	6 (5.1—6.9)

*$p = 0.105$, **log-rank = 9.7; $p = 0.008$, ***log-rank = 38.6; $p = 0.000$.

Table 8 The effect of developing local disseminations on the survival times of the patients

Local dissemination development	Median survival time (month) (95% CI)	*p*
Local dissemination developed	9 (8.0—10.0)	Log-rank = 0.17; *p* = 0.6385
Not developed local dissemination	10 (7.4—12.6)	

4. Discussion

The LD frequency of the tumor at sites where an invasive procedure has been performed over the chest wall has previously been shown to range between 2% and 51%, with a median value of approximately 20% in MPM patients [11—13]. Whereas, in secondary cancers of pleura, the similar dissemination rate is low and the mentioned local RP is not recommended [14,15]. In this study consisting of 212 patients the LD frequency was 13.2%, and that patients had short survival rates irrespective of whether they developed LD.

Previous reports have indicated that although the resulting LD does not have a negative impact on prognosis, it may diminish the quality of life in MPM patients in terms of side effects such as pain and difficulty sleeping [2,16]. Therefore, the use of PR is still commonly accepted. During PR, a low dose (21 Gy administered within a week) and a narrow application field is used, ensuring a short procedure time with few complications [2,17]. It has been hypothesized that PR may generate an environment that is not suitable for the development of LD [2]. It is recommended that PR is applied immediately after the invasive procedure (within 1—4 weeks) [2,4,6,18,19]. An increase in the rate of LD frequency has been reported in cases where a longer application onset time [18,19] or a lower dose (for example, 10 Gy) was used [20].

Application of PR in order to prevent LD is an easy procedure, and although the complication rate is low, PR could both be a waste of time and money in MPM-specialized clinics. A limited number of studies have evaluated the guidelines that recommend PR administration as Grade A Evidence in MPM patients [4,6,21]. Both retrospective [22] and randomized [2] studies based on these guidelines recommend the use of PR. In contrast, it has been reported by a randomized study of 61 patients who PR was not useful in preventing LD after chest drain or pleural biopsy in patients with malignant mesothelioma, and that a higher frequency of LD was observed in the group that received PR [23]. In another randomized study, it has been observed that PR did not decrease the LD frequency in both groups [20]. However, in these randomized studies, only a limited amount of data concerning the usefulness of PR and its absolute recommendation can be obtained. In another consensus report, it has been established that sufficient evidence did not exist in order to recommend PR [21]. Since the guideline recommendations [4,6] for the use of PR stem from a single study [2] consisting of a limited number of subjects, meta-analysis of available trial data are required.

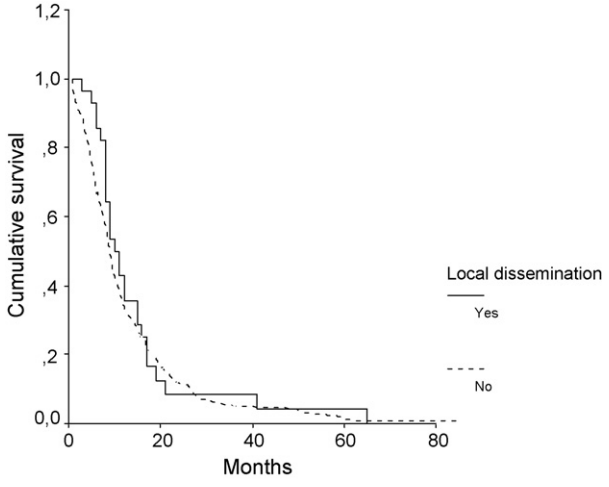

Fig. 1 Kaplan—Meier curves comparing the median survival times in patients with or without LD.

The factors that determine whether LD will develop in MPM patients are still unclear. It is not known whether the cell type of the tumor affects the development of LD. Furthermore, the effects of invasive procedures, form of treatment, disease stage, and gender of the patient on the rate of LD development have not been fully addressed [4,13,20,21,24]. Determining which patients would be suitable candidates for receiving PR would be beneficial in terms of time and money.

Here, we found that the LD frequency was not associated with the gender of the patient or the disease stage. We show that LD develops more frequently in patients who received thoracotomy as an invasive procedure than in patients who received thoracoscopy and CT-CPNB or CPNB. We have previously reported an LD rate of 21.7% in MPM patients where CT-CPNB with a Ramel or Abrams biopsy needle was performed for diagnostic purposes (the procedure was carried out twice for some subjects) [25]. In another study which investigates the function of image-guided core needle biopsy, thoracoscopy and thoracotomy in MPM, and the frequency of LD complication, the LD rate was established as 4% with image-guided core biopsy with a 14—20 gauge cutting needle, and 22% after surgical biopsy [13]. Authors show that patients who receive image-guided needle biopsy have a longer survival rate than patients treated with surgery (who have a higher incidence of LD) [13]. In a group of patients who received video thoracoscopic surgery, an LD development rate of 50% has previously been reported [26]. In this study, we show that the frequency of LD differs depending on the diagnostic procedures used, and that the risk of developing LD was higher after thoracotomy. In addition, we observe a difference between the appearance times of LD based on the invasive procedure type. Thus, we conclude that an increased LD rate, which depends on the risk of having a greater number of malignant cells, is due to the

incision width during the procedure and is not associated with a longer survival time.

The relationship between the histopathological type of tumor and the LD frequency has not been reported. We found that the frequency of LD was 10.8% in patients with epithelial cell type, 12.9% in patients with mixed type, and 23.8% in patients with sarcomatous-type tumors, suggesting that the LD frequency depends on the histopathological type of tumor. Although these findings were not statistically significant, they show that the LD frequency in sarcomatous-type tumors was twice as high as others. We observed a longer survival time in patients with epithelial cell-type tumors and found that the LD appearance time was longer in these tumors than in mixed and sarcomatous cell-type tumors (7 months versus 2 months).

The low LD rates are possible in patients using chemotherapy regimes with high response rates [7—9] (Table 7). The frequency of LD is low (4.9%) in patients with objective response to chemotherapy, is 10% in patients with stable disease. Although the frequency of LD is rather high in patients with progressive disease (18.2%), appearance time is 5 months, median survival is just 6 months for this patient group (Table 7).

We evaluated whether the type of treatment a patient received could affect the LD frequency. Here, we found that the LD frequency after multi-modal treatment was double the frequency observed in patients receiving chemotherapy and supportive treatment, although this difference was not statistically significant (23.1% versus 11.8%). While the LD appearance time in patients receiving supportive treatment was quite short (2 months), the appearance time in patients with multi-modal treatment was 12 months. The median survival times in patients receiving multi-modal treatment was significantly longer than in patients treated by other methods (16 months), suggesting that the treatment type affects the LD frequency. The high LD rate in patients receiving multi-modal treatment might depend on two factors: the first one is the fact that these subjects live longer. In the second one is the used of thoracotomy. Thoracotomy might account for increased LD risk as another influencing factor (Table 3).

The data in this study are a new basis for a critical discussion of previous and premature recommendations. We can state that a general recommendation for PR is not justified and PR may be considered in special patient groups.

In order to prevent the development of LD in MPM patients, we propose that PR can be administered 4 weeks following the diagnosis in patients with sarcomatous cell type, independent of the procedure used during treatment or diagnosis. Although the LD rate in mixed cell-type tumors was not as high as in the sarcomatous cell type, PR can also be recommended for this group as the appearance time is approximately 2 months. In patients with epithelial cell-type tumors, PR can be administered in cases where the patients will receive only supportive follow up treatments or in patients where thoracotomy is applied only for diagnostic purposes without multi-modal treatment. We propose that PR is initially unnecessary in patients with epithelial cell-type tumors who will receive chemotherapy treatment. PR is not required in patients with epithelial cell-type tumors once it has been established that they do not respond to chemotherapy, since the median survival time is 6 months, and the median LD appearance time is 5 months in these patients.

In conclusion, the incidence of LD in this series was lower than in previous reports, thus questioning general recommendations for PR. Highly selected patient groups such as those receiving supportive therapy, who underwent thoracotomy without multi-modal therapy, or patients with sarcomatous and mixed cell-type tumors may be considered for PR in an individual approach.

Conflict of interest

None.

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