ANTICANCER RESEARCH *39*: 839-845 (2019)
doi:10.21873/anticanres.13183

Malignant Peritoneal Mesothelioma: Treatment Options and Survival

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Abstract. *Background: Malignant peritoneal mesothelioma (MPeM) is a rare type of cancer with a poor prognosis. Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) have been shown to improve survival. Treatment and survival of patients with MPeM have not been previously studied in Finland. Materials and Methods: The data consisted of all patients diagnosed with MPeM during years 2000-2012 in Finland, including cancer notifications, death certificates and information about asbestos exposure. Results: Among 50/94 (53.2%) patients treated for MPeM, 44/50 (88.0%) were treated palliatively, 4/50 (8.0%) with radical surgery and chemotherapy, and 2/50 (4.0%) with CRS plus HIPEC. Five-year survival was 50.0% for those treated with CRS plus HIPEC and 75.0% for those treated with radical surgery and chemotherapy. Radical surgery with chemotherapy was associated with significantly longer survival compared to radiation (p=0.008), chemotherapy and radiation (p=0.043), surgery, chemotherapy and radiation (p=0.039), and palliative surgery (p=0.009). Conclusion: Treatment of MPeM is heterogenic in Finland. CRS plus HIPEC, and radical surgery with chemotherapy seem to increase the survival. Patients considered candidates for radical surgery should be sent to specialized centers for further assessment.*

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Key Words: Mesothelioma, peritoneal mesothelioma, treatment, survival, Finland, CRS, HIPEC, chemotherapy, radiotherapy, asbestos exposure.

The annual incidence of malignant peritoneal mesothelioma (MPeM) has been reported to be 0.2 to 3 cases per 1,000,000 people per year, globally (1). In our previous study, the incidence of MPeM was 0.74 cases per 1,000,000 people per year in Finland. The median survival time after diagnosis of MPeM in Finland was 4 months (2).

In the 1990s, cytoreduction combined with intraperitoneal chemotherapy was considered for patients with peritoneal mesothelioma (3). Since then, cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is a treatment reported increasingly with promising long-term survival in highly selected patients (4). Implementing this treatment modality has improved the 5-year survival rate to 50% in this patient group (5). Despite these advances in treatment, it has been noted that globally, the majority of patients with MPeM receive only palliative care or systemic chemotherapy (6), leaving many eligible patients without the benefit of this more invasive treatment modality. This phenomenon is noted in our previous study, in which the majority of patients were treated with palliative therapy or diagnosed during autopsy (2).

The primary aim of this study was to identify first-line treatments given to patients who were diagnosed with MPeM in Finland between the years 2000 and 2012 from medical records. We also assessed the effectiveness of the different treatment modalities given to these patients. The secondary aim was to clarify the effect of different treatment modalities on different histological subtypes and in patients exposed to asbestos.

Materials and Methods

This was a retrospective study involving all Finnish patients with MPeM diagnosed between 1st of January 2000 and 31st of December 2012. Basic information, means of diagnosis, distribution of the

disease, histological subtypes and asbestos exposure of the patients were described earlier (2). In brief, data were collected from the Finnish Cancer Registry and Statistics Finland including cancer notifications and histological subtypes, death certificates and spreading of the disease. The patients' diagnostic procedures and treatment were identified from their medical records, which were obtained from all public hospitals with permission. Types of surgical procedures performed, different first-line chemotherapeutic agents used and total radiation doses given were clarified from the patients' medical records. Additionally, we checked patient survival collectively in May 2018 from the Population Register Center and Statistics Finland. Information about previous asbestos exposure and insurance decisions concerning occupational diseases was collected from the National Workers' Compensation Center. In addition, differences in survival according to histological subtype were studied.

A total of 94 patients were diagnosed with MPeM between 1st of January 2000 and 31st of December 2012. Forty patients (42.6%) did not receive cancer-aimed treatment, and received only palliative or no treatment at all. These patients were excluded from this study since the aim of the study was to evaluate the efficacy of various given treatments. Four patients (4.3%) were excluded from the study as they did not have primary MPeM: two with origin from tunica vaginalis testis, one from pleura, and one patient with peritoneal disseminated adenocarcinoma that was originally misdiagnosed as MPeM.

Statistical analysis. The data were collected, and analyzed using IBM SPSS Statistics version 24 for Mac (IBM, Armonk, NY, USA). Different treatment options were compared with each other by chi-square tests and with Fisher's exact test. Correlation was calculated by Pearson's correlation coefficient. Survival was calculated with Kaplan–Meier graphs. A p-value of less than 0.05 was regarded as significant.

Ethics. This study was approved by the Heart and Lung Center of Helsinki University Hospital, the National Institute of Health and Welfare, Statistics Finland, and as well by the Ethical Committee of Helsinki and Uusimaa Hospital District, approval numbers §31, 22.03.2013; THL/989/5.05.00/2013; TK-53-862-13; 418/13/03/02/15, respectively.

Results

Altogether, 50 out of the 94 patients diagnosed with MPeM (53.2%, male 33/60, female 17/34) received some kind of operative, chemotherapeutic or radiation treatment. Basic patient characteristics are presented in Table I.

There was no statistically significant association between sex and given treatment (p=0.090), nor with survival (p=0.402).

Treatment methods. First-line chemotherapy was the most used treatment modality. The chemotherapeutic agents used varied and are presented in Figure 1.

Other ways of treatment used were radiation only, surgery (radical, palliative, CRS plus HIPEC) and combinations of the above treatment methods (Table II). In radiation therapy, radiation doses used ranged between 12 and 30 Gy.

Table I. *Basic information of patients with malignant peritoneal mesothelioma*.

Variable	Total	Male	Female
Median age (years)	61.5 (24-88)	61	64
Disease extent, n			
Local	2	2	0
FRLN	29	18	11
DM	1	1	0
Unknown	18	12	6
Histological subtype, n			
Epithelial	19	12	7
Sarcomatoid	2	2	0
Biphasic	4	3	1
Unknown	25	16	9
Asbestos exposure, n			
Yes	11	9	2
No	21	11	10
Unknown	18	13	5
Diagnosis, n			
PTH	37	20	17
MH	4	4	0
Obduction	8	8	0
Clinical	1	1	0
Total	50	33	17

FRLN: Further than regional lymph nodes; DM: distant metastasis; PTH: primary tumor histology; MH: metastatic histology.

Fifteen out of the 50 patients (30.0%) had undergone surgery during their treatment. The number of radical operations including peritonectomy was six, of which two were with and four without HIPEC. Radical operations included radical cytoreductive resection of the tumor and peritonectomy. The number of palliative operations was nine, including resection of omentum, resection of resectable tumor during explorative laparotomy, Hartman operation, ileotransversostomy and abdominal hysterectomy with bilateral salpingo-ophorectomy. Among two of the patients treated with palliative surgery, chemotherapy and radiation were combined in the treatment.

In all of the radically operated cases, adjuvant systemic chemotherapy was given. Chemotherapeutic agents used were pemetrexed combined with carboplatin or with cisplatin. In CRS with HIPEC, after radical peritonectomy and macroscopically radical resection, HIPEC was performed with mitomycin or the combination of doxorubicin and cisplatin.

Survival. With a median survival of 62 months, radical surgery with chemotherapy was related to a longer survival, compared to radiation (p=0.008), chemotherapy with radiation (p=0.043), palliative surgery with chemotherapy and radiation (p=0.039), and palliative surgery (p=0.009). CRS with HIPEC, with a median survival of 40 months, was

Table II. *Different treatment options used in the treatment of patients with malignant peritoneal mesothelioma.*

Treatment	Patients, n (%)	Male, n	Female, n	Median age (range) of diagnosis, years
Ctx	24/50 (48.0%)	13	11	61 (53-75)
Palliative surgery	7/50 (14.0%)	6	1	67 (55-81)
CRT	6/50 (12.0%)	6	0	55 (37-74)
RT	5/50 (10.0%)	3	2	75 (56-88)
Radical surgery + Ctx	4/50 (8.0%)	3	1	61 (24-67)
CRS + HIPEC	2/50 (4.0%)	2	0	62 (57-66)
Palliative surgery + CRT	2/50 (4.0%)	0	2	40 (27-52)

Ctx: Chemotherapy; RT: radiotherapy; CRT: chemotherapy with radiotherapy.

not significantly associated with better survival compared to other treatments. Different treatment options are compared pairwise concerning survival in Table III. Median survival and survival percentages according to different treatment options after 1, 3 and 6 months, and 1 and 5 years are presented in Table IV. Survival rates according to the use of different chemotherapeutic agents are presented in Figure 1.

Extent of disease. Proportions of different treatment options according to disease distribution are presented in Figure 2. Exact information about the level of disease spread was available for 32 out of the 50 patients (64.4%). There was no significant association between survival and the level of spread.

Histology. Information on the histological subtype was available for 25 out of the 50 cases (50.0 %), of which 19/25 (76.0%) were epithelial, 2/25 (8.0%) sarcomatoid, and 4/25 (16.0%) were biphasic type. Median survival time after diagnosis was nine (range=2-92) months in those with epithelial MPeM, 1 (range=1-8) month in those with sarcomatoid MPeM, and 2 (range 1-68) months in those with biphasic MPeM. The epithelial subtype was associated with better survival compared to the sarcomatoid subtype (p=0.039). The proportions of treatments used according to histological subtype are presented in Figure 3. Extent of disease among different histological subtypes is presented in Figure 4.

Asbestos exposure. Information about whether there was previous exposure to asbestos was available for 32 out of the 50 patients (64.0%), of whom 7/32 (21.9%) had a history of asbestos exposure. Median survival time after diagnosis of patients with asbestos exposure was 8 (range 2-58) months, while it was 40 (range 1-92) months for patients without exposure. Asbestos exposure was associated with worse survival (p=0.025). Histological subtypes of patients exposed and not exposed to asbestos are presented in Figure 5.

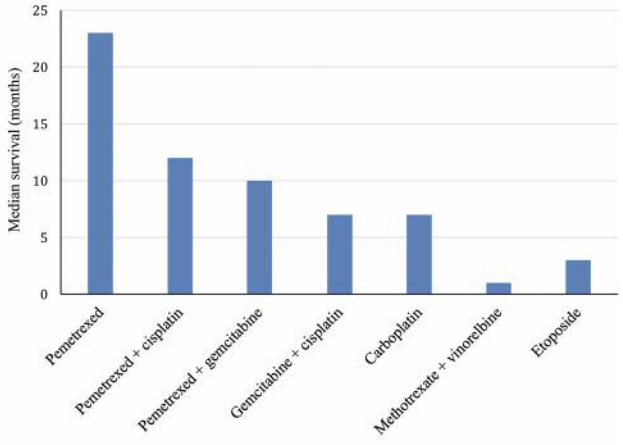

Figure 1. *Different chemotherapeutic agents and their effect on survival.*

Discussion

In our study, the treatment methods of MPeM were shown to be heterogenic and varied widely. The most prevalent treatment methods were chemotherapy and palliative surgery. Radical surgery with chemotherapy and CRS with HIPEC were associated with superior overall survival. To our laudable, treatment of MPeM and its effect on survival in Finland is reported here for the first time.

In our study, patients with radical surgery reached a 5-year survival of 50.0% with HIPEC and 75.0% without HIPEC. The survival rates of patients treated with CRS plus HIPEC are in accordance with earlier studies (7-12). An interesting observation was that survival results for patients not treated with HIPEC were even better than for those treated with HIPEC. The reason for this remains unclear since the distribution and histological subtypes did not differ for these patients. The small number of patients treated with CRS plus HIPEC in our study is due to the facts that HIPEC was not performed in Finland until 2007 and there was a small number of MPeM cases in Finland during the study period.

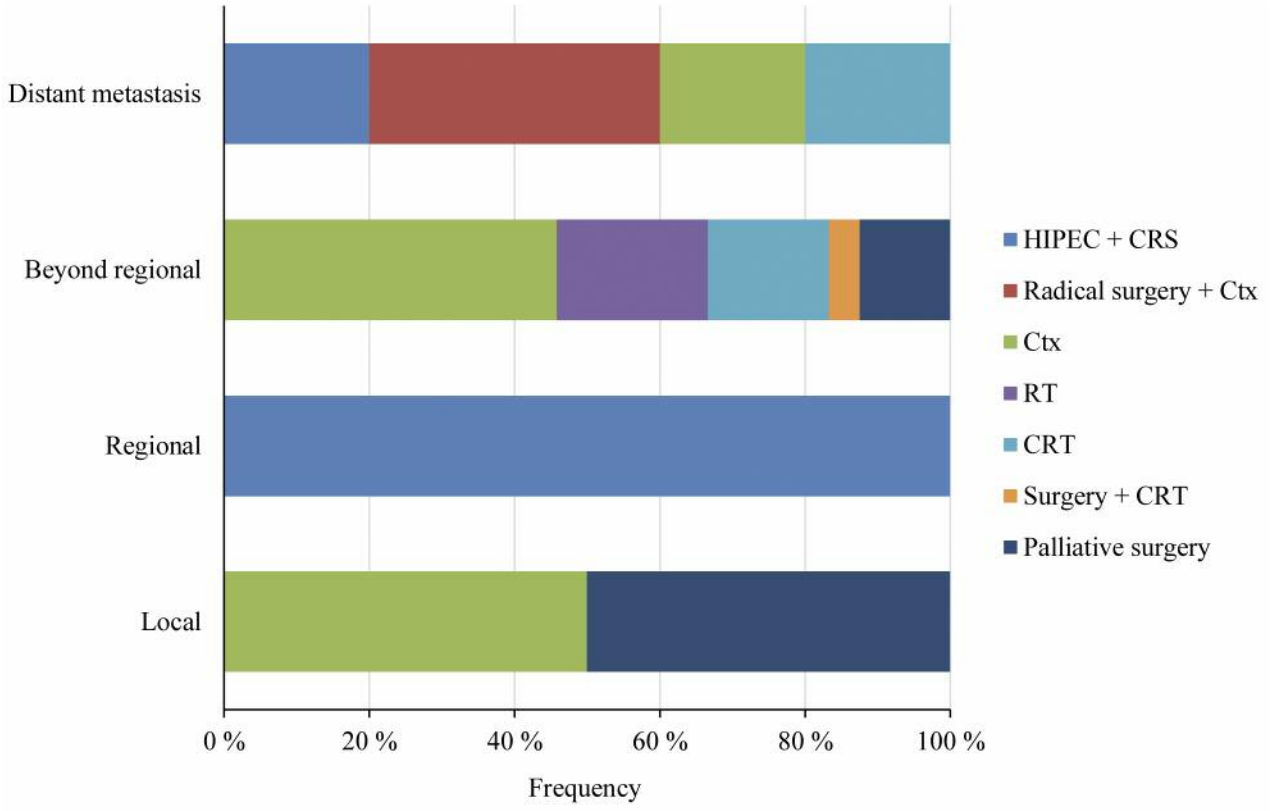

Figure 2. *Disease extent and treatment methods used. Ctx: Chemotherapy; RT: radiotherapy; CRT: chemotherapy with radiotherapy.*

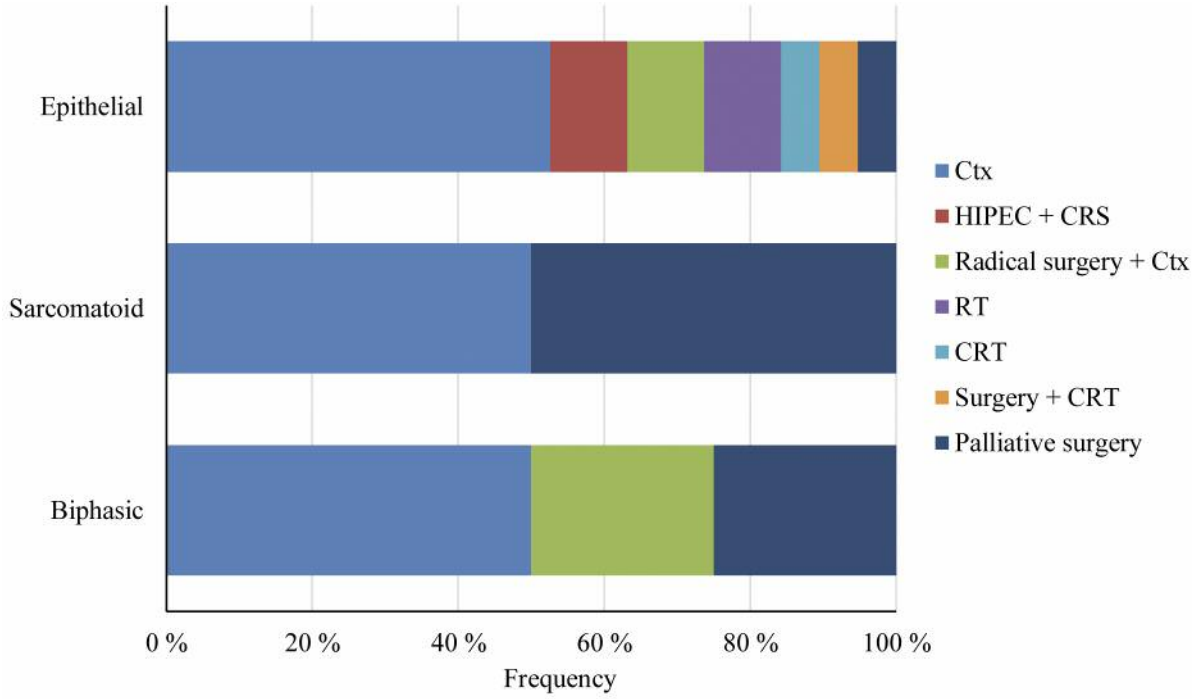

Figure 3. *Proportions of used treatments on different histological subtypes of malignant peritoneal mesothelioma among patients. Ctx: Chemotherapy; RT: radiotherapy; CRT: chemotherapy with radiotherapy.*

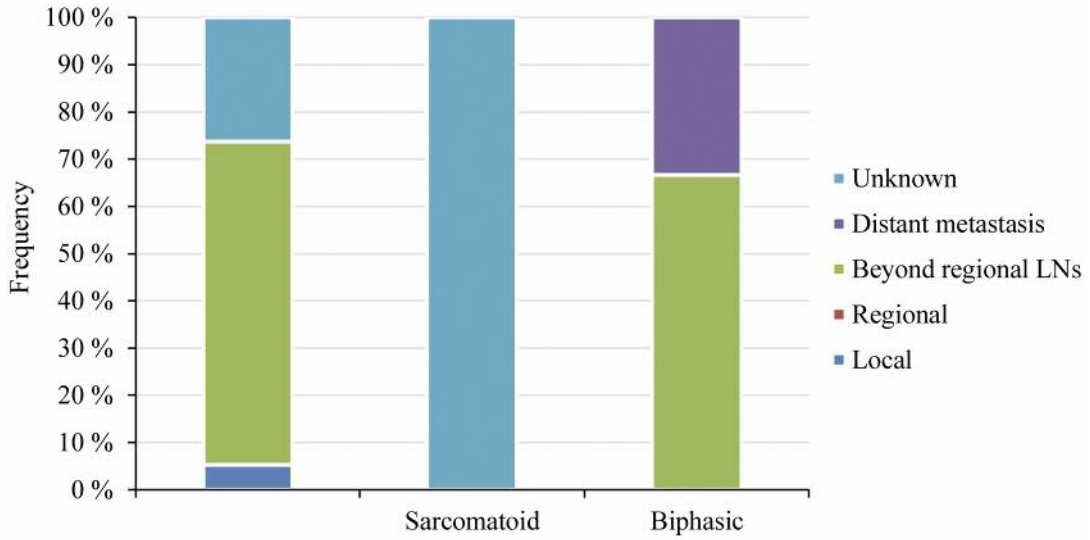

Figure 4. *Levels of distribution among different histological subtypes of patients with malignant peritoneal mesothelioma. LNs: Lymph nodes.*

In addition, the small number of cases in each patient group may cause statistical bias when comparing different treatment methods. Today, CRS combined with HIPEC is recommended as a first-line treatment for patients with an operable tumor and who can tolerate the planned procedure (13).

Systemic chemotherapy increased the 6-month survival to 79.2%, but did not extend the long-term survival. Previous reports also stated that systemic chemotherapy was of palliative benefit, however, not improving survival (14). Systemic chemotherapy is considered as an alternative therapy for inoperable patients (15). Pemetrexed and the combination of pemetrexed and cisplatin led to the best prognoses, with median survival of 23 and 12 months, respectively. Similar results were found in earlier literature (16). Pemetrexed with cisplatin or carboplatin is considered as standard first-line systemic chemotherapy (15). In earlier studies, pemetrexed and gemcitabine were shown to increase survival, however, with a response rate not greater than 15% (17).

In the present study, radiation and palliative surgery were not associated with longer survival, as neither of these measures were aimed to reduce the overall tumor burden. Earlier literature states that the efficacy of radiation for MPeM is unclear (18). MPeM was shown to be resistant to radiation therapy alone, but radiation appeared to be more effective when combined with radical surgery and intraperitoneal chemotherapy (19, 20). In addition, unresectable MPeM can be treated with the combination of chemotherapy, radiotherapy and immunotherapy (21).

Epithelial MPeM was associated with the best survival among all histological subtypes, while sarcomatoid and biphasic MPeM had worse prognosis, with no significant difference in this study. However, the small number of patients with histological subtypes may have biased the results. In earlier literature, the epithelial subtype of MPeM was identified as a favorable prognostic factor (18, 22). None of the patients with sarcomatoid subtype were treated with radical surgery nor with CRS with HIPEC. In earlier literature, the sarcomatoid subtype was associated with worse prognosis (23). Magge *et al*. stated that aggressive histologies, such as sarcomatoid and biphasic subtypes may not benefit from CRS with HIPEC (24).

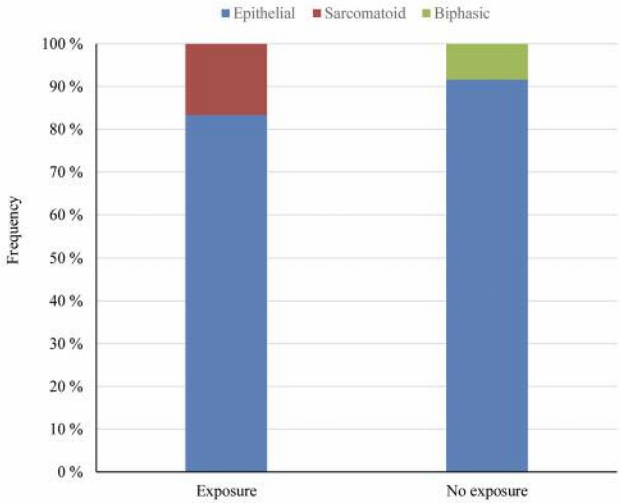

Figure 5. *The histological subtypes of patients with malignant peritoneal mesothelioma with and without asbestos exposure.*

Table III. *Survival results after diagnosis compared pairwise with Fisher's exact test, endpoint 60 months. Significant p-values are shown in bold.*

Treatment	HIPEC +CRS	Radical surgery + Ctx	Ctx	RT	CRT	Palliative surgery + CRT	Palliative surgery
HIPEC+CRS		0.083	0.683	0.090	0.758	0.225	0.112
Radical surgery+Ctx	0.083		0.185	**0.008**	**0.043**	**0.039**	**0.009**
Ctx	0.683	0.185		**0.037**	0.805	0.233	0.014
Radiation	0.090	**0.008**	**0.037**		0.103	0.926	0.968
CRT	0.758	**0.043**	0.805	0.103		0.366	0.034
Palliative surgery+CRT	0.225	**0.039**	0.233	0.926	0.366		0.838
Palliative surgery	0.112	**0.009**	0.014	0.968	**0.034**	0.838	

Ctx: Chemotherapy; RT: radiotherapy; CRT: chemotherapy with radiotherapy.

Table IV. *Median survival and survival percentages after diagnosis in patients with malignant peritoneal mesothelioma treated with different treatment options.*

		Survival at (%)				
Treatment	Median survival (range), months	1 Month	3 Months	6 Months	1 Year	5 Years
HIPEC+CRS	40 (40-40)	100%	100%	100%	100%	50.0%
Radical surgery+Ctx	62 (57-68)	100%	100%	100%	100%	75.0%
Ctx	9 (0-92)	95.8%	87.5%	79.2%	45.3%	20.8%
RT	2 (2-15)	100%	20.0%	20.0%	20.0%	0.0%
CRT	8 (1-58)	100%	83.3%	83.3%	50.0%	0.0%
Surgery+RT	2 (2-9)	100%	50.0%	50.0%	0.0%	0.0%
Palliative surgery	1 (1-18)	100%	57.1%	42.9%	28.6%	14.3%
Total	8 (0-92)	98.0%	76.0%	70.0%	46.0%	20.0%

Ctx: Chemotherapy; RT: radiotherapy; CRT: chemotherapy with radiotherapy.

The limitations of our studies are its retrospective setting and the relatively small number of patients. However, in previous publications, the treatment of MPeM has mostly been examined through retrospective, single-institutional studies (25). No randomized controlled trials have been published on treatment options for MPeM (25). Our study deals with the experience of the whole country and several institutions, which can be considered as a strength of our study.

Conclusion

In conclusion, MPeM is a rare disease and almost half the patients remain untreated. HIPEC with CRS and radical surgery with chemotherapy seem to increase the long-term survival. Treatment methods may be diverse due to the rarity of the disease and difficulties in diagnostics. Therefore, patients considered candidates for radical surgery should be sent to specialized centers for further assessment.

Conflicts of Interest

The Authors have no conflicts of interest to declare in regard to this study.

Acknowledgements

Silja Salo received a personal grant from the Finnish Cultural Foundation's North Savo Regional Fund. The study was supported by the Cancer Society of Finland and the Finnish Work Environment Fund.

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Received December 11, 2018
Revised December 19, 2018
Accepted December 21, 2018