Original article

Results of treatment of 33 patients with peritoneal mesothelioma

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Background: Peritoneal mesothelioma is a rare peritoneal malignancy, representing approximately one-third of all mesotheliomas. It is regarded as a universally fatal cancer with few treatment options.

Methods: Records of 33 patients with peritoneal mesothelioma were reviewed retrospectively. Demographic, clinical and quantitative prognostic indicators were evaluated and analysed statistically using survival as endpoint. Patients were treated by a uniform strategy involving cytoreductive surgery with peritonectomy procedures and perioperative intraperitoneal chemotherapy (cisplatin, doxorubicin).

Results: There were ten women and 23 men; mean age was 53·0 years. Asbestos exposure was recorded in five patients and a family history of cancer in 13. Presentation was mainly abdominal distension and pain. Median survival was 31·0 months; overall projected survival at 3 years was 56 per cent. The most significant positive predictive factors of survival were: female sex ($P = 0·003$), low prior surgical score ($P = 0·002$), completeness of cytoreduction ($P = 0·0002$) and second-look surgery ($P = 0·019$). The morbidity rate for this combined treatment was 33 per cent and the perioperative mortality rate was 3 per cent.

Conclusion: Although peritoneal mesothelioma is rare, progress in its management has occurred. Survival has been extended and selection factors by which patients may be allocated to aggressive management strategies have been defined.

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Introduction

Mesothelioma is a neoplasm originating from the mesothelial surface lining cells of the serous human body cavities. Mesothelioma may involve the pleura, less frequently the peritoneum and, rarely, the pericardium and the tunica vaginalis testis. Peritoneal mesothelioma is usually a rapidly fatal peritoneal surface malignancy with a median survival of less than 1 year[1]. It represents about one-third of all forms of mesothelioma[1–3]. Several articles have appeared in the medical literature on the asbestos–mesothelioma aetiological link since Wagner *et al.*[4] first described this important relationship in 1960. Implication of asbestos exposure in the causation of peritoneal mesothelioma is far less obvious than in pleural mesothelioma[1,5]. This report describes an experience with 33 patients with peritoneal mesothelioma, and analyses their clinicopathological features. Treatment consisted of a combined approach of extensive cytoreductive surgery with peritonectomy procedures and intraperitoneal perioperative chemotherapy[6,7]. This aggressive therapeutic approach resulted in successful palliation of ascites and long-term survival was seen in some patients. A search was made for selection factors associated with an improved quality of life and a prolonged survival for patients with peritoneal mesothelioma.

Patients and methods

Patients

The records of 58 patients with primary peritoneal surface malignancy surgically treated between 1989 and 1999 were reviewed retrospectively. Thirty-seven patients with peritoneal mesothelioma were identified together with 13 patients with primary peritoneal adenocarcinoma and eight patients with papillary serous carcinoma of the peritoneum.

This report was restricted to 33 patients with mesothelioma involving exclusively the peritoneum, free from distant metastasis at the time of initial treatment at this institution.

Pathology

Pathological procedures included examination of haematoxylin and eosin-stained sections, routine histochemistry and, when required, specialized immunohistochemical tests for differentiation from other peritoneal surface malignancies. The immunohistochemical stains included mucicarmin alcian blue, monoclonal antikeratin antibodies CAM5.2 and AE1/3, epithelial membrane antigen, carcinoembryogenic antigen (CEA), carcinogenic antigen 125 (CA125), tumour-associated glycoprotein B72.3, monoclonal antibody Ber-EP4, antimyelomonocytic antibody Leu-M1, placental alkaline phosphatase and acid calcium-conjugated S-100 protein.

Clinical features analysed

The following data were retrieved from the patient records and analysed for their impact on survival: age at surgery, sex, race, personal and familial medical history, exposure to asbestos, and use of tobacco and alcohol. From other institutions were gathered date and character of first presenting symptom, date of first diagnosis, previous surgery and adjuvant treatments before referral.

A series of quantitative prognostic indicators for peritoneal surface malignancy was used in an attempt to identify selection factors for treatment: the prior surgical score, the peritoneal cancer index and the completeness of cytoreduction score. All these indicators used survival as an endpoint. The prior surgical score has been described previously[8] and ranged from zero to 3 (0, no previous surgery; 1, one abdominopelvic region dissected; 2, two to four regions dissected; 3, five or more abdominal regions). The peritoneal cancer index visually assessed the mass of tumour present within the abdomen and pelvis at the time of abdominal exploration. It has also been described previously[9]. It quantified the tumour in 13 abdominopelvic regions by a lesion size score; the size of the largest nodule and not the number of lesions was scored. The lesion size was from zero to 3 (1, lesion smaller than 0·5 cm; 2, lesion smaller than 5 cm; 3, lesion larger than 5 cm or layering of mesothelioma in the region); the maximum peritoneal cancer index was 39 (3×13). The completeness of cytoreduction score is another quantitative visual assessment of tumour volume left on the peritoneal surface[8]. In contrast to the peritoneal cancer index, which was scored during abdominal exploration, this scoring occurred after the surgical efforts had been completed. The score ranged from zero to 3 (0, no tumour; 1, nodules smaller than 0·25 cm; 2, nodules smaller than 2·5 cm; 3, nodules larger than 2·5 cm remaining after surgery or confluent tumour); complete cytoreduction was reflected by a score of 0 or 1. Performance status was assessed using the Zubrod–Eastern Co-operative Oncology Group (ECOG) scale from zero to 5, with zero indicating a normal level of function[10]. The following data were recorded from patients' charts and follow-up notes: physical examination and operative findings, surgical procedures, intraoperative and postoperative intraperitoneal chemotherapy treatments, postoperative course and treatments including systemic chemotherapy and radiation, second- and third-look operative procedures, tumour marker levels, presence or absence of metastasis, survival status, date and cause of death.

Treatments

The goal of the treatment was to use both surgery and regional chemotherapy maximally in every patient, to the limits of patient tolerance[11]. Nine patients with extensive ascites were treated before surgery with induction intraperitoneal chemotherapy using cisplatin (Platinol; Bristol Myers Squib Company, Pennington, New Jersey, USA) at 15 mg per m^2 per day and doxorubicin (Adriamycin; BenVenue Laboratories, Bedford, Ohio, USA) at 6 mg per m^2 per day. Each cycle of treatment was for 5 consecutive days, given once a month for 3 months. After the induction intraperitoneal chemotherapy the patients went on to cytoreductive surgery. The other 24 patients' initial treatment at this institution was cytoreductive surgery, which included all or part of the following five peritonectomy procedures, which have been described previously: greater and lesser omentectomy, right and left subphrenic peritonectomy and complete pelvic peritonectomy[6]. Visceral resections were often required for complete cytoreduction. During the surgical procedure the patients had intraoperative intraperitoneal chemotherapy with cisplatin 50 mg/m^2 and doxorubicin 15 mg/m^2, heated to 41–41·5°C[12]. Patients who had a moderate-to-large volume of mesothelioma left behind after surgery were treated with additional cycles of postoperative intraperitoneal chemotherapy, with a similar dose and schedule to the induction treatment. Toxicity was recorded and graded according to the National Cancer Institute Common Toxicity Criteria[13]. Follow-up was updated until 15 August 1999.

Statistical analysis

Survival was retained as endpoint for all statistical analysis, and was determined from the time of initial diagnosis. The

survival curves were obtained using the Kaplan–Meier method and comparison of survival was by log rank test[14,15]. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Demographic and epidemiological data

The significant data are summarized in *Table 1*. The mean age was 53·0 (range 17–79) years. There was a statistically significant advantage in survival for women: median 41 *versus* 16 months for men ($P = 0.003$). Thirty-one patients were Caucasian; there was one African American and one Asian American. Twelve patients had no history of exposure to asbestos, five had a positive history (two worked in a shipyard, one in a cement factory, one with insulation and one as an electrician) and there were no data on 16 patients. Six patients were tobacco users. The alcohol consumption rate was low (four patients) and no patient used recreational drugs. Thirteen patients had a family history of cancer (in a parent or sibling), five of whom had more than one first-degree relative with a malignancy.

Symptoms, signs and diagnosis

The commonest initial complaints for peritoneal mesothelioma, isolated or combined, were an increasing abdominal girth (22 patients), abdominal pain (nine) and weight loss (six). Ascites was present at time of diagnosis in 22 patients and was debilitating in six (*Table 1*). Unusual presentations included acute abdomen (one) and rectal bleeding (one). The mean interval from onset of symptoms to diagnosis was 5 (range 0–33) months. The mean interval from diagnosis to definitive cytoreduction was 9 (range 1–48) months. Diagnosis of peritoneal mesothelioma was made by laparotomy in 18 patients, by laparoscopy in ten, and by abdominal puncture and cytology in five patients.

Treatments before definitive cytoreduction and intraperitoneal chemotherapy

Sixteen patients received chemotherapy before cytoreductive surgery: intraperitoneal (nine), systemic (seven) and both (two). These chemotherapy treatments before and after cytoreductive surgery were not part of a systematic perioperative approach, but reported as treatments received at different institutions. No patient underwent irradiation. Induction intraperitoneal chemotherapy was successful in eight of nine patients but there was no significant impact on survival (*Table 1*). The performance status before cytoreduction was zero or 1 in 21 patients and 2–4 in 12 patients; their median survival was 29 and 17 months respectively ($P = 0.029$). The prior surgical score was zero in 18 patients and 1–3 in 15 patients; the median survival was 41 and 16 months respectively ($P = 0.002$) (*Table 1*).

Table 1 Significant epidemiological and clinical data on 33 patients with peritoneal mesothelioma

	No. of patients	Median survival (months)	P*
Age (years)			0·21
≤ 53	16	28	
> 53	17	17	
Sex			0·003
Female	10	41	
Male	23	16	
Asbestos exposure			0·49
Yes	5	16	
No	12	16	
Unknown	16	33	
Ascites			0·61
Yes	22	17	
No	11	34	
Debilitating	6	28	
Precp. chemotherapy			0·55
Systemic	7	34	
Intraperitoneal	9	35	
Both	2	51	
Performance status			0·03
0–1	21	29	
2–4	12	17	
Prior surgical score			0·002
0	18	41	
1–3	15	16	

Survival was measured from the time of diagnosis. *Log rank test

Treatment data

Significant data regarding treatments are shown in *Table 2*. Between 1989 and 1999, 47 cytoreductive procedures were performed on 33 patients with peritoneal mesothelioma by the same surgeon: 33 as a first procedure, 11 as second-look and three as third-look surgery. Twenty of the 33 patients had the first cytoreduction after 1995. Twenty patients received a major first cytoreduction involving four or more abdominopelvic regions. Thirteen patients, with high comorbidity or irresectable peritoneal mesothelioma, had a less extensive debulking procedure; a comparison of survival approached statistical significance in favour of major cytoreduction ($P = 0.07$). Mean operating time was 6·8 (range 2–13·5) h; mean ascites volume was 2·4 (range 0–14) litres; mean blood requirement was 2 (range 0–8) units. For the initial 33 cytoreductions the mean peritoneal cancer index was 29. For patients with a score of 0–28 the median survival was 34 months compared with only 16 months for patients with a score between 29 and 39;

Table 2 Significant treatment data on 33 patients with peritoneal mesothelioma

	No. of patients	Median survival (months)	P*
Cytoreduction			0·07
Major	20	38	
Minor	13	15	
Peritoneal cancer index			0·026
0–28	17	34	
29–39	16	16	
Completeness of cytoreduction score			0·0002
0–2	17	41	
3	16	13	
Perop. intraperitoneal chemotherapy			0·11
Yes	28	28	
No	5	18	
Second-look surgery†			0·019
Yes	11	35	
No	22	16	
Metastasis			0·001
Yes	7	17	
No	21	28	
Unknown	5	11	
Status			
No evidence of disease	8	38	
Alive with disease	10	23	
Dead from disease	15	16	

Survival was measured from the time of diagnosis. *Log rank test

the peritoneal cancer index was a statistically significant predictor of survival ($P = 0.026$). The completeness of cytoreduction score was 0–2 in 17 patients and 3 in 16 patients, with a median survival of 41 and 13 months respectively ($P = 0.0002$). Twenty-eight patients received perioperative intraperitoneal chemotherapy (heated intraoperative treatment, postoperative treatment or both) and five patients did not; their median survival was 28 and 18 months respectively ($P = 0.11$). Eleven patients had a scheduled second-look cytoreduction 6–9 months after the first operation, combined with perioperative intraperitoneal chemotherapy in ten. Three patients had a third-look operation. Median survival was 35 months in the 11 patients who had second-look surgery compared with 16 months in the other 22 patients; this was statistically significant ($P = 0.002$), although the survival advantage may have resulted from selection factors inherent to that group of patients.

Morbidity and mortality

There were 11 patients with grade III–IV complications, giving an overall morbidity rate of 33 per cent. Four patients required reoperation for persistent bile leak from the liver surface (one), small bowel fistula (one) and late intra-abdominal bleeding (two). There was one perioperative death from sepsis that occurred 33 days after surgery.

Table 3 Pathology of peritoneal mesothelioma

	No. of patients	No evidence of disease	Alive with disease	Dead from disease
Multicystic	2	2	0	0
Adenomatoid multicentric	1	1	0	0
Epithelial				
Epithelioid	10	2	3	5
Tubulopapillary	17	3	7	7
Biphasic	2	0	0	2
Sarcomatous	1	0	0	1
Total	33	8	10	15

Pathological features

Thirty-three patients retained a diagnosis of peritoneal mesothelioma (*Table 3*): 30 malignant, two low-grade malignant multicystic mesotheliomas and one multicentric aggressive adenomatoid mesothelioma. The malignant mesothelioma subtypes were epithelial in 27 patients, subdivided into ten epithelioid and 17 tubulopapillary lesions, biphasic or mixed in two patients and sarcomatous in one. All three patients with mesothelioma of low malignant potential are free from disease; the three patients with an aggressive subtype have died from the disease, and patients with epithelial histology showed a mixed response to treatment.

Follow-up and survival

The median follow-up after cytoreduction was 21·3 (range 1–79) months. No patient was lost to follow-up. During follow-up distant metastases were later diagnosed in seven patients: liver (one), mediastinum (one), lung (two) and pleural cavity (three). All patients who developed distant metastasis have died from the disease. Twenty-one patients had no metastasis and there were no data on five patients (*Table 2*). The occurrence of metastasis decreased survival significantly ($P = 0.001$).

Fifteen patients died from the disease and 18 patients are still alive (*Table 2*). Ten are alive with disease and eight have no evidence of disease by imaging, tumour markers and second- or third-look surgery. The median survival from diagnosis was 31·0 months. The Kaplan–Meier survival curve for this group is shown in *Fig. 1*. The projected overall survival at 1, 3 and 5 years is 77, 56 and 47 per cent respectively.

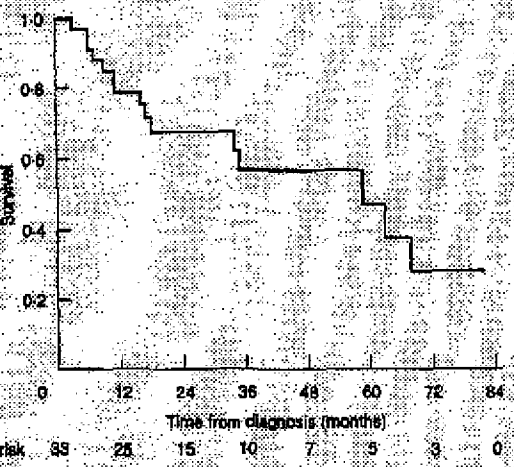

Fig. 1 Kaplan–Meier survival curve of 33 patients with peritoneal mesothelioma. Median survival from diagnosis was 31·0 months

Discussion

Peritoneal mesothelioma has evolved over almost 100 years from a clinical oddity to an established rare disease of increasing importance. In 1908 Miller and Wynn[16] first described '...a malignant tumour arising from the endothelium of the peritoneum and producing mucoid ascitic fluid.' In 1909 Adami[17] first used the term mesothelioma to refer to a highly malignant tumour of the serosal membranes involving mostly the pleura and the peritoneum, and less often the pericardium and tunica vaginalis testis. Mesothelioma is not specific to humans and is also found in other mammalian species, including horse, monkey, dog and cow[18–20]. The link between mesothelioma and exposure to asbestos is widely accepted; its incidence is increasing in the industrialized nations[21,22]. Peritoneal mesothelioma represents 20–37 per cent of all mesotheliomas[1–3]; because of its rarity and the small size of published series, an estimation can only be made of 200–400 new cases annually in the USA. Four histological types of malignant peritoneal mesothelioma are recognized: epithelial (75 per cent), sarcomatous, mixed or biphasic and poorly differentiated; multicystic and multicentric adenomatoid peritoneal mesothelioma has a malignant potential[23–25].

In a review of the literature no dominant therapeutic guideline for peritoneal mesothelioma was found. Few articles were clinicopathological retrospective reviews and most were case reports compiling disparate and deceptive therapeutic experiences, including use of systemic chemotherapy, whole abdomen irradiation, and intraperitoneal treatments with compounds such as colloidal radioactive ^{32}P and ^{198}Au, thiotepa and bleomycin[3,26,27]. More recent reports show a more systematic approach to peritoneal mesothelioma, with debulking surgery and systemic chemotherapy with paclitaxel, cisplatin alone or doxorubicin[28–30]. A phase I trial with 18 patients reported a similar approach to the present one, with promising preliminary results[31]. The prognosis is grim after diagnosis of peritoneal mesothelioma: survival of 7–13·5 months and only a few long-term survivors are reported[1,3,26,32,33]. The median survival in this group was 31·0 months from diagnosis, with a projected 3-year survival of 56 per cent. These results need to be tempered by the relatively short follow-up after cytoreduction.

In this study, positive predictive factors of survival were identified by univariate analysis: (1) female sex, (2) good health status, (3) minimal previous surgery, (4) low peritoneal cancer index, (5) low completeness of cytoreduction score and (6) second-look surgery (for selected patients); these factors correlated with improved survival. There was a suggestion that partial debulking or resection of mesothelioma in the absence of intraperitoneal chemotherapy may jeopardize subsequent treatment. Patients who had a high prior surgical score were not as likely to survive long term. The peritoneal surface malignancy may be moved more rapidly to an invasive process if anatomical defences are destroyed by surgery. In patients who had trocar-site tumour progression, the abdominal wall masses progressed more rapidly than residual tumour in the abdomen.

Patients in whom major resection of the mesothelioma was possible, reflected by a low completeness of cytoreduction score, survived statistically longer. Patients with minimal or no progression of disease and no systemic component of mesothelioma were candidates for a second-look reoperation. In this selected group the survival was significantly prolonged. These findings suggest, but do not confirm, that aggressive cytoreductive surgery is of value in this group of patients and should be recommended.

There was no statistical indication that intraperitoneal chemotherapy resulted in survival benefit. It is possible that selection factors were important in this evaluation, because patients with a large volume of mesothelioma after cytoreduction were usually not given intraperitoneal chemotherapy. However, it may be unwise to conclude that intraperitoneal chemotherapy may be eliminated from the treatment regimen. Compared with previous experience with this disease, the benefits of intraperitoneal chemotherapy in palliation were thought to be substantial. All but one patient had no further symptoms from ascites after cytoreduction and perioperative intraperitoneal chemotherapy. In the group of patients with resection of gross disease (completeness of cytoreduction score 1 or 2)

intraperitoneal chemotherapy may have been an essential component of the treatment that resulted in long-term survival. With the current state of knowledge, a recommendation for intraperitoneal cisplatin and doxorubicin as a standard treatment for peritoneal mesothelioma, combined with cytoreductive surgery, may be worthy of consideration.

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