International Journal of Hyperthermia

ISSN: 0265-6736 (Print) 1464-5157 (Online) Journal homepage: http://www.tandfonline.com/loi/ihyt20

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To cite this article: Konstantinos Stamou, Dimitrios Tsamis, Nikolaos Pallas, Evangelia Samanta, Nikolaos Courcoutsakis, Panos Prassopoulos & Antonios-Apostolos Tentes (2015): Treating peritoneal mesothelioma with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. A case series and review of the literature, International Journal of Hyperthermia, DOI: 10.3109/02656736.2015.1075071

To link to this article: http://dx.doi.org/10.3109/02656736.2015.1075071

Published online: 18 Sep 2015.

International Journal of Hyperthermia

http://informahealthcare.com/hth
ISSN: 0265-6736 (print), 1464-5157 (electronic)

Int. J. Hyperthermia, Early Online: 1–7
 DOI: 10.3109/02656736.2015.1075071

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RESEARCH ARTICLE

Treating peritoneal mesothelioma with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. A case series and review of the literature

Konstantinos Stamou[1], Dimitrios Tsamis[1], Nikolaos Pallas[1], Evangelia Samanta[2], Nikolaos Courcoutsakis[3], Panos Prassopoulos[3], & Antonios-Apostolos Tentes[1]

[1]Department of Surgical Oncology, Metropolitan Hospital, Athens, Greece, [2]Department of Anaesthesiology, Metropolitan Hospital, Athens, Greece, and [3]Department of Radiology, Democritus University of Thrace, Greece

Abstract

Background: Encouraging results on survival of patients with malignant peritoneal mesothelioma have been shown with the use of cytoreductive surgery and perioperative intraperitoneal chemotherapy. This study explores the impact of aggressive surgical treatment on overall survival of peritoneal mesothelioma. *Methods*: This is a retrospective analysis of prospectively collected clinical data of all patients with diagnosis of malignant peritoneal mesothelioma treated in a designated referral centre in Greece. All patients were offered cytoreductive surgery and intraperitoneal chemotherapy. Patient's characteristics, operative reports, pathology reports, and discharge summaries were stored in an electronic database and later reviewed and analysed. *Results*: Cytoreduction for peritoneal mesothelioma was performed on 20 patients (15 men and 5 women) with a mean age of 59.4 years (SD 16.1). Mean peritoneal cancer index was 16.1 (SD 10.4) and the median completeness of cytoreduction score was 2 (range 1–2). Mean overall survival was 46.8 months (SE 4.03) with a mean of 21.4 and median of 18 months of follow-up. Disease-specific survival was 100% for the observed period. Univariate analysis showed the completeness of cytoreduction as the only possible predictor of survival. A median of 10 (range 4–14) peritonectomy procedures were performed per patient. Median hospital stay was 14 (range 10–57 days). Grade III and IV complications occurred post-operatively in 5 patients (25%). Two patients died in the post-operative period of pulmonary embolism and myocardial infarction. *Conclusion*: Cytoreductive surgery with HIPEC has proved the most effective treatment even when taking account of the cost of significant morbidity.

Keywords

HIPEC, intraperitoneal chemotherapy, mesothelioma, surgical cytoreduction

History

Received 19 April 2015
Revised 11 July 2015
Accepted 16 July 2015
Published online 16 September 2015

Introduction

Diffuse malignant peritoneal mesothelioma (DMPM) is a highly aggressive tumour that develops from the mesothelial lining of the peritoneum. The incidence is estimated at 300–400 new cases per year in the USA, while an increase of the actual incidence is recorded worldwide [1]. In Greece it is estimated that 5–10 new cases per year will occur, with most research focused on pleural mesothelioma [2]. Long-term exposure to the various forms of asbestos is connected to the majority of cases of pleural and peritoneal mesothelioma maybe in synergy with infection with the simian virus 40 [3–5]. Millions of people have been exposed to asbestos in the past and DMPM is expected to develop approximately 20–30 years after initial exposure, somewhat earlier than the development of pleural mesothelioma [3,6]. However, in many cases no occupational or other risk factor can be identified.

Correspondence: Dr Konstantinos Stamou, Department of Surgical Oncology, Metropolitan Hospital, 15 Lykeiou street, 10674, Athens, Greece, Fax: 00302107237518. E-mail: cstamou@hotmail.com

Systemic therapies of patients with malignant peritoneal mesothelioma have not shown to be effective in improving overall and disease-free survival. In historical controls median survival rarely exceeds 1 year [7,8]. Since the introduction of cytoreductive surgery with perioperative intraperitoneal chemotherapy preferably given in the form of heated intraoperative intraperitoneal chemotherapy (HIPEC), a substantial increase of overall survival has been reported [9,10]. This was officially presented in the first National Institute of Health Peritoneal Mesothelioma Conference in 2004 [11]. The concept behind cytoreductive surgery is that by resecting all macroscopic disease and by eradicating microscopic residual disease with intraperitoneal chemotherapy, the greatest possible chance for cure is given to the patient (Figure 1). This presupposes that the disease is actually locoregional, behaves like it, and that there is substantial response to the chemotherapy agent that is used. The peritoneal malignant mesothelioma generally develops and stays in the peritoneal cavity making the disease an ideal model for these combined treatment strategies (Figure 2). Reported 5-year survival rates after cytoreductive surgery and

HIPEC of peritoneal malignant mesothelioma range widely from 29–93% [9,12–14].

The aim of this study is to present the experience of a referral centre for peritoneal surface malignancy in Greece in treating malignant peritoneal mesothelioma by cytoreductive surgery and HIPEC.

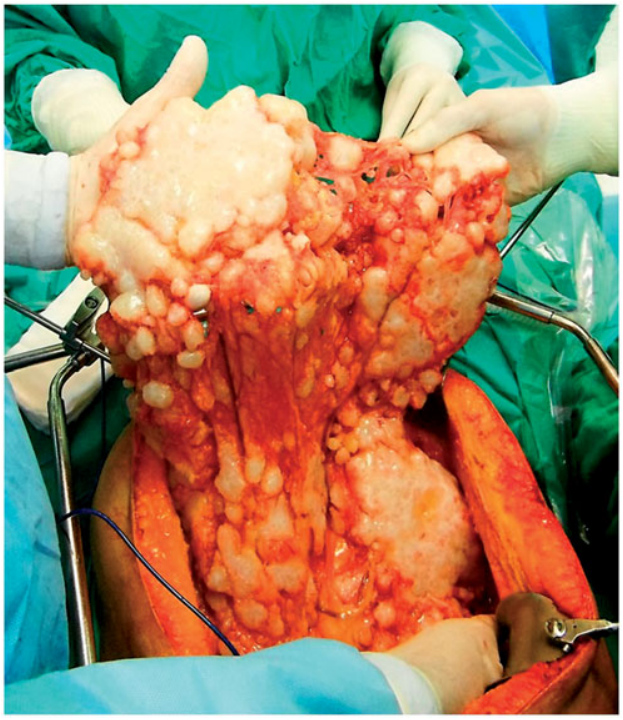

Figure 1. Malignant peritoneal mesothelioma in the form of 'omental cake'. Despite the impressive appearance, these lesions are resectable.

Patients and methods

This is an observational cohort study of all patients that were referred to a designated centre for peritoneal surface malignancy between 1999 and 2014 with an initial diagnosis of DMPM. Data were collected and maintained prospectively in a prototype electronic database customized for peritoneal surface malignancy patients. All patients were offered cytoreductive surgery and perioperative intraperitoneal chemotherapy by a qualified surgical team. The senior author was present for all operations. Institutional scientific and ethics committee approval was obtained for performing cytoreductive surgery, collecting data, and reporting although individual patients are not identifiable.

Patient characteristics, operative reports, pathology reports, discharge summaries and morbidity/mortality data were reviewed and analysed.

Eligibility criteria

Diagnosis was confirmed preoperatively in all patients with biopsies taken after laparotomy, laparoscopy, or computed tomography (CT)-guided, usually by the referring physician. Patients were offered surgery if mesothelioma was confined to the abdomen without distant metastases. Abdominal CT and CT enteroclysis was used to assess the spread of the disease on the surface and the mesentery of the small bowel [15]. Gross infiltration of the mesentery and multiple nodules on the anti-mesenteric edge of the small bowel that would require several segmental resections were considered possible exclusion criteria and these patients had diagnostic laparoscopy prior to definite surgery. On laparoscopy the small bowel was assessed and a decision to proceed or not was taken. Patients were stratified according to Karnofsky performance status (KPS) into three groups: 100–90, 89–70

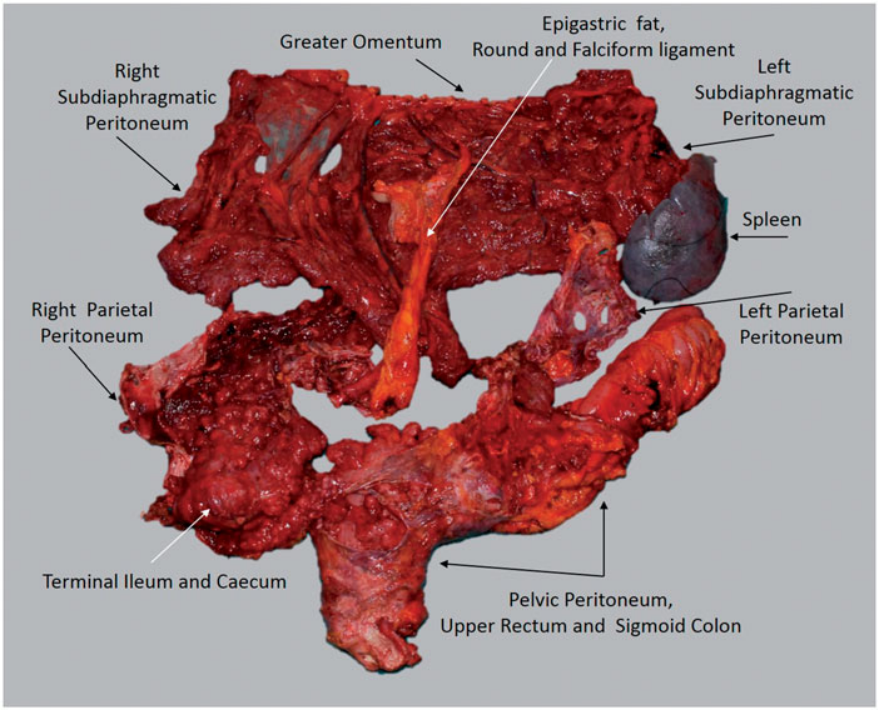

Figure 2. Surgical specimen of cytoreductive surgery for malignant peritoneal mesothelioma. Great care is taken to resect the affected organs and peritoneal surfaces 'en bloc'.

and 69–50. Patients with a KPS < 50 were excluded from surgical treatment.

Assessment of prior surgical intervention

The prior surgical score (PSS) is an assessment of the extent of all prior surgical procedures [16]. To quantitate PSS, the abdomen and pelvis are divided into nine regions and the number of regions previously dissected estimated from old operative reports. PSS-0 indicates biopsy only, PSS-1 minimal prior dissection with only one abdominal region dissected; PSS-2 indicates 2–5 regions dissected and PSS-3 extensive prior cytoreduction with more than three regions dissected.

Abdominal exploration

As the abdomen was explored, the peritoneal cancer index (PCI) was recorded. PCI is a clinical integration of both peritoneal implant size and distribution of peritoneal surface malignancy [16]. To assess PCI, the abdomen and pelvis were divided into 13 anatomical regions. The size of the largest malignant nodule per region was scored. The summation of the lesion size score in all of the 13 regions was the PCI for the individual patient. Standard peritonectomy procedures were performed aiming for complete cytoreduction [17]. Combined organ resection was performed when this was necessary, to achieve a zero score for completeness of cytoreduction (CC-0) operation or when surgical palliation was desired.

Completeness of cytoreduction score

At the completion of the surgical procedure a completeness of cytoreduction score (CC) was recorded. A CC-0 score indicates that no peritoneal seeding was visible after the cytoreduction, CC-1 indicates residual tumour nodules less than 2.5 mm, CC-2 indicates residual tumour nodules 2.5 mm to 2.5 cm and a CC-3 score indicates persistent tumour nodules greater than 2.5 cm [16]. Patients with a CC-3 score did not receive intraperitoneal chemotherapy.

Intraperitoneal chemotherapy

HIPEC with the Coliseum technique was always administered after tumour resection and before the reconstruction of the alimentary tract. HIPEC was possible with a continuous closed circuit of four drains (two inlet and two outlet), one heat exchanger, and two roller pumps connected to the inlet and outlet drains (Sun-Chip, Gamida Tech, Eaubonne, France) [16]. The cytostatic drugs were diluted in 2–3 L of Ringer's lactate solution and the intra-abdominal temperature was maintained at 42.5–43.0 °C during perfusion. Cisplatin (50 mg/m^2) in combination with doxorubicin (15 mg/m^2) were used in chemotherapy naïve patients for 90 min [16]. Early post-operative intraperitoneal chemotherapy (EPIC) was performed with 5-fluorouracil (400 mg/m^2) as a five-day peritoneal lavage as described in Sugarbaker's manual [16]. Patients with grossly inadequate cytoreduction did not receive intraperitoneal chemotherapy. Only EPIC was given to the first two patients that were treated when hyperthermia was not available in our hospital. HIPEC and EPIC were subsequently given to the next two patients when hyperthermia became available. Thereafter all patients were given HIPEC.

Systemic chemotherapy

Patients were stratified according to whether they had received neo-adjuvant chemotherapy or not. All patients were referred to attending oncologists for systemic chemotherapy after the operation and their recovery.

Pathology characteristics

Tumour volume was characterised as 'large' or 'small' according to the size of nodules that were observed intraoperatively. Cases with a lesion score equal to or greater than 2 (>0.5 cm) were considered large tumour volume [16]. For the purpose of the present analysis, peritoneal mesothelioma was categorised into low-grade (including multicystic mesothelioma) and high-grade (including epithelial, biphasic and sarcomatoid mesothelioma) [18,19].

Follow-up assessment

Follow-up evaluation of all living patients was performed mainly by direct interview, and when not possible, over the phone. Attending physicians were contacted as needed. Follow-up consisted of abdominal and chest CT scans, complete blood count, serous markers (CEA, Ca19-9, Ca 125) and clinical examination every 4 months for the first year and every 6 months thereafter. Information on deceased patients was collected from the follow-up database, and by contacting patients' relatives and physicians. No patients were lost to follow-up.

Statistical analysis

The end point of the study was survival. Statistical analysis included Student's t-test for comparisons of mean values. The most significant predictor for survival from univariate analysis was used to stratify the Kaplan-Meier survival curves. Survival curves were tested with a log-rank test. All statistical analyses were performed on a personal computer with the statistical package IBM® SPSS® 22.0 for Windows (Chicago, IL). Statistical significance for p, was fixed at equal or less than 0.05 as standard.

Results

Cytoreduction for peritoneal mesothelioma was performed on 20 patients (15 men and 5 women), with a mean age of 59.4 years at the time of the operation (SD 16.1, range 16–73 years). Mean overall survival was 46.8 months (SE 4.03) with a mean of 21.4 and median of 18 months of follow-up. Disease-specific survival is 100% for the observed period of 52 months. No loss of follow-up occurred. Three operations were assessed as CC-3 and the patients did not receive HIPEC and were considered as having residual disease in the follow-up. Another three patients recurred in 11, 16 and 19 months respectively.

Table 1 itemizes different possible prognostic factors and their impact on survival and intra-abdominal recurrence. As shown in the table, none of the parameters examined

Table 1. Analysis of clinical features prior to surgery and their impact on survival.

Clinical features	n (%)	Significance	*p*
Sex		ns	0.571
Female	5 (25.0)		
Male	15 (75.0)		
Age (median: 59)		ns	0.234
>70	7 (35.0)		
<70	13 (65.0)		
Performance status		ns	0.572
100–90	7 (35.0)		
80–70	7 (35.0)		
60–50	6 (30.0)		
Tumour volume		ns	0.382
Large	5 (25.0)		
Small	15 (75.0)		
Tumour grade		ns	0.470
High	17 (85.0)		
Low	3 (15.0)		
Prior surgical score		ns	0.804
PSS-0	4 (20.0)		
PSS-1	11 (55.0)		
PSS-2	1 (5.0)		
PSS-3	4 (20.0)		
Neo-adjuvant chemotherapy		ns	0.700
Yes	2 (10.0)		
No	18 (90.0)		

Table 2. Analysis of clinical features and treatment and their impact on survival.

Clinical features and treatment efforts	n (%)	Significance	*p*
Peritoneal cancer index (median 17)		ns	0.234
≥17	12 (66.6%)		
<17	8 (33.4%)		
Complete cytoreduction score		s	0.000
CC-0	9 (45.0%)		
CC-1	7 (15.0%)		
CC-2	1 (5.0%)		
CC-3	3 (15.0%)		
Intraperitoneal chemotherapy			
HIPEC	13 (65.0%)		
HIPEC + EPIC	2 (10.0%)		
EPIC	2 (10.0%)		
Not performed	3 (15.0%)		
Systemic chemotherapy		ns	0.470
Performed	5 (25.0%)		
Not performed	15 (75.0%)		

(sex, age, KPS, tumour volume and grade, and neo-adjuvant chemotherapy) affected survival or local recurrence.

Table 2 analyses the impact of clinical features and treatment modalities on survival and intra-abdominal recurrence. Univariate analysis revealed the CC score as the only possible predictor of survival.

Clinical information gained intraoperatively

Mean PCI was 16.1 (SD 10.4, range 3–39), the median CC score was 2 (range 1–2). Median operative time was 8 h. Transfusion requirements reached a median of 1 (range 0–4) units of packed red cells (PRC) and 4 (range 0–8) units of fresh frozen plasma (FFP) per patient. None of these clinical features or treatments had an impact on survival. Thirteen patients received only HIPEC and only EPIC was prescribed for another two. A combination of the two was performed in two patients while three patients did not receive any intra-peritoneal chemotherapy since the cytoreduction was determined as CC-3. When HIPEC was used in combination with EPIC, no benefit for survival was evident.

A median of 10 (range 4–14) peritonectomy procedures were performed per patient. The right and left diaphragms were stripped in 13 and 10 patients respectively. The right and left lateral parietal peritoneum in 13 and 11 patients. The greater and lesser omentum was resected in 15 and 12 patients and the omental bursa in nine. Small bowel resection was necessary in two patients while partial gastrectomy was performed in four. Splenectomy was performed in nine, cholecystectomy in nine, pelvic peritonectomy in 16 and total hysterectomy in three patients. Small bowel resections were necessary in two, partial gastrectomy in three and colectomy in eight patients. Mesenteric deposits needed cauterisation in six. Neither had an impact on survival in these patients with carcinomatosis.

Median hospital stay was 14 days ranging from 10 to 57 days. Grade III and IV complications occurred post-operatively in five patients (20%). Two patients died in the post-operative period, one of pulmonary embolism and one of myocardial infarction. One patient developed short gut syndrome and required prolonged parenteral nutrition.

Discussion

Malignant peritoneal mesothelioma is a relatively rare malignancy. This explains in part why experience in treating it was limited, and overall survival very poor. Survival was closely associated with specific subtypes of the disease and chemotherapy was generally used as palliative care. A better understanding of the disease came with the concentration of cases to designated referral centres where combined multi-modality treatments eventually led to better overall survival [12,20,21]. The fact that the disease was connected to recognised occupational health hazards raised substantial legal issues connected to financial compensation. This also contributed to a push for more research on an otherwise ‘orphan disease’.

Pathogenesis

It is believed that the risk of developing peritoneal mesothelioma increases proportionally to the cumulative exposure to asbestos. It is also estimated that the malignant mesothelioma requires a median of 3.75 years of exposure to asbestos to develop [3]. Pathogenic mechanisms that play a role in the development of malignant mesothelioma are the generation of reactive oxygen species and the depletion of antioxidants. Crocidolite asbestos fibres, especially, oxidise thioredoxin-1, an antioxidant, and further, activate inflammasomes in mesothelial cells [3,4]. Newer studies have revealed that viruses such as Simian virus 40 (SV40) have oncogenic potential and act synergistically with asbestos for DNA damage and malignant transformation in peritoneal mesothelial cells [5].

Clinico-pathological prognostic factors

Age and sex of the DMPM patients have been proposed as possible prognostic factors for overall survival. In a study of 294 patients from the Peritoneal Surface Oncology Group International (PSOGI), female patients were shown to have a significantly improved survival outcome but older female patients fared significantly worse than younger females [22]. The rationale behind this finding may lay in the findings of Pinton et al. [23], who explored the prognostic significance of oestrogen receptor (ER) expression in 78 patients with malignant pleural mesothelioma and found the expression of ERb (but not ERa) receptors to be an independent predictor of improved survival. Because of the small number of women used in our study it probably failed to show a significant trend in the analysis.

Approximately one third of the patients typically presented with abdominal pain and/or increasing abdominal girth. Other symptoms included a new onset hernia and a variety of other clinical symptoms such as anorexia, dyspnoea, fever and abdominal mass. The heterogeneity of these clinical symptoms generally delays diagnosis [24].

Mesothelioma presents in three main histological forms: epithelioid, sarcomatoid and biphasic [19]. The most common form is epithelioid mesothelioma while the biphasic subtype shows a mixture of both epithelioid and sarcomatoid features and is seen in about 25% of patients. The pure sarcomatoid subtype is rare and more aggressive, with very few cases reported in the literature. Rarer varieties include the benign adenomatoid tumour and the borderline tumours (well-differentiated papillary mesothelioma and multi-cystic mesothelioma) [19].

Of the various pathological factors that have been examined, the size of the nucleus and the mitotic count have proved significant for prognosis [25,26]. These findings were confirmed by Yan et al. [27], who showed that the 3-year survival rates with nuclear size of 10–20, 21–30, 31–40 and >40 μm were 100%, 87%, 27% and 0%, respectively. Lymph node metastases from malignant mesothelioma are not common (<6%) but when present are associated with poor survival [12]. Subsequently, there is no standard lymphadenectomy procedure involved in the surgical strategy.

Preoperative assessment

The eligibility of a DMPM patient to have comprehensive treatment with cytoreduction and HIPEC depends largely on two parameters. First, the patient's KPS is required to be high enough to withstand treatment. In cytoreductive surgery the post-operative morbidity is expected to reach the levels of 25–40%. Older patients and patients with significant co-morbidities do not fare well in the occurrence of complications. Second, the distribution of the disease in critical anatomical areas will prohibit CC while increasing the risk of surgical complications. Areas of the abdomen that may not be cleared of all visible disease are the mesentery and the anti-mesenteric edge of the small bowel and the hepato-duodenal ligament. CT has been found to effectively identify excessive disease on crucial anatomic sites and helps in avoiding unnecessary laparotomies [28]. Still, decision-making on the grounds of preoperative abdominal CT has no actual effect on survival, as was shown by the work of the Italian National Cancer Institute in Milan [20]. Our group has developed and tested a modified technique of CT enteroclysis that showed 92% sensitivity, 96% specificity, 97% PPV, and 91% NPV in assessing peritoneal carcinomatosis in the small bowel mesentery [15].

Treatment

Historically, mesothelioma patients had poor survival rates of less than 1 year [7,8]. A major drawback in previous decades was the fact that peritoneal spread was considered by surgeons and oncologists alike as an 'unresectable disease'. The evolution of surgical techniques that enabled stripping of the parietal peritoneum and removal of affected organs replaced the concept of 'debulking' and its inherent palliative logic with the concept of 'cytoreduction' that has curative intent [17]. Given the fact that DMPM is predominantly a locoregional peritoneal surface disease, cytoreductive surgery seems to offer a theoretical advantage. The greatest input for this surgical technique came from Sugarbaker [10] who provided a comprehensive corpus of teaching material so that his results could be reproduced independently.

Intraperitoneal administration of chemotherapy secures a higher local concentration of the chemotherapeutic agent compared to aggressive doses of systemic chemotherapy. Amplified cytotoxicity is achieved with hyperthermia that has an independent effect on cells [29]. The effectiveness of several chemotherapy agents has been studied although it is considered exceptionally difficult to provide solid results in cohort studies. The reason is that the researchers would need large numbers of standardised patients that have received more or less similar surgery. This is not easy to achieve as peritoneal carcinomatosis presents with a considerably wide spectrum of disease not to mention irregularities in the quality of surgery and post-operative care. In such a multi-factorial system derived from an already rare disease, it is very difficult to isolate the importance of a single chemotherapy agent. Alexander et al. [30] showed than intraperitoneal cisplatin may offer a survival advantage over mitomycin C alone. Cisplatin and carboplatin with the addition of doxorubicin or mitomycin C have shown encouraging results with improved overall, disease-free and progression-free survival and shorter hospital stay [31,32]. These agents are most commonly used and were used by our team in accordance with the relevant literature. For EPIC, initial results with the use of 5FU were not encouraging and research focused on paclitaxel. Recently, pemetrexed (used before for adjuvant intraperitoneal chemotherapy in combination with cisplatin) has been tried as systemic treatment for pleural and peritoneal mesothelioma patients with favourable results [33,34].

Morbidity and mortality

Cytoreduction with HIPEC is a major and complex procedure performed on cancer patients with correspondingly high morbidity and mortality. Mortality in 30 days after operation in several studies has been recorded in the range of 1.9–8% while major post-operative morbidity varied from 25–40% [12–14,21,35]. In our study similar results were recorded in terms of post-operative morbidity. The post-operative

mortality appears high since a fatal DVT-PE and a myocardial infarction raised it to 10%. We believe this to be random as it is not reproduced in the greatest cohort of peritoneal surface patients from our institution.

Survival

The breakthrough in the treatment of mesothelioma was evident in the early 1990s when surgery was combined with EPIC, with cisplatin, and etoposide [36]. In studies from referral centres the median overall survival varies from 34 to 92 months and median progression-free survival is approximately 25.1 months. Probability of 5-year survival in studies with median follow-up of 37–72 months was 29–59% [9,12,14,21]. In the study by Baratti et al. [37] of 108 patients with median follow-up of 48.8 months the survival curve reached a plateau after 7 years representing 43.6% of actual survivors. In the largest multicentre study so far, that enrolled 405 patients, the overall median survival was 53 months, and 3- and 5-year survival rates were 60% and 47% respectively [12]. Cytoreduction should be carried out to the level of CC-0 or CC-1, a finding in agreement with the concept of HIPEC [12,20,35].

Experience from specialised centres on DMPM will continue to be recorded and analysed in order to exact precise and detailed results which will help to outline the appropriate therapeutic protocols. So far, cytoreductive surgery with HIPEC has proved to be an effective and safe treatment for peritoneal mesothelioma. A better combination of chemotherapy agents and possibly new drugs will help mesothelioma patients survive a very aggressive disease.

Declaration of interest

The authors have no conflicts of interest or financial ties to disclose. The authors alone are responsible for the content and writing of the paper.

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