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Treatment Factors Associated With Long-Term Survival Following Cytoreductive Surgery and Regional Chemotherapy for Patients with Malignant Peritoneal Mesothelioma

H. Richard Alexander Jr, M.D.[1], **David L. Bartlett, M.D.**[2], **James F. Pingpank, M.D.**[2], **Steven K. Libutti, M.D.**[3], **Richard Royal, M.D.**[3], **Marybeth S. Hughes, M.D.**[3], **Matthew Holtzman, M.D.**[2], **Nader Hanna, M.D.**[1], **Keli Turner, M.D.**[1], **Tatiana Beresneva, M.D.**[3], and **Yue Zhu, M. D., M.S.**[1]

[1]The Divisions of General and Oncologic Surgery (Maryland) [2]Surgical Oncology (Pittsburgh), Departments of Surgery, University of Maryland School of Medicine, Baltimore, and the University of Pittsburgh Medical Center, Pittsburgh [3]Surgery Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland

Abstract

OBJECTIVES—Malignant peritoneal mesothelioma (MPM) is a primary cancer that arises diffusely from the serosa of the peritoneum. Morbidity and mortality are almost invariably due to loco-regional progression; cytoreduction with intra-operative or peri-operative high dose regional chemotherapy has been established as the preferred approach in selected patients. This study was performed to identify factors associated with long-term outcome.

METHODS—Between January, 1992 and 2010, 211 patients with MPM treated at three major referral centers with operative cytoreduction and hyperthermic intra-operative peritoneal chemotherapy (HIPEC) were analyzed.

RESULTS—The median actuarial overall survival was 38.4 months; the actuarial 5 and 10 year survivals were 41% and 26%, respectively. On multivariate analysis, factors independently associated with favorable outcome were age less than 60 years ($p< 0.01$), complete or near complete ($R_{0–1}$) versus incomplete ($R_{2–3}$) resection ($p< 0.02$), low versus high histologic grade ($P< 0.01$), and the use of cisplatin versus mitomycin-C during HIPEC ($p< 0.01$). There was an insignificant trend towards female gender and improved survival (male Hazard Ratio: 1.46, 95% CI: 0.89–2.41, p=0.13).

CONCUSIONS—Operative cytoreduction with HIPEC is associated with long term survival in patients with MPM. Factors associated with survival include age, complete or near complete gross tumor resection, histologic tumor grade, and HIPEC with cisplatin. The fact that cisplatin versus mitomycin-c was independently associated with improved survival demonstrates a salutary effect for HIPEC with cisplatin in the management of patients with MPM.

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Address correspondence to: H. Richard Alexander, Jr., M.D., Division of General and Oncologic Surgery, Department of Surgery, University of Maryland School of Medicine, 22 S. Greene Street, Baltimore, Maryland 21201, HRAlexander@smail.umaryland.edu.

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Introduction

Malignant peritoneal mesothelioma or MPM is a rare and ultimately fatal cancer arising from the mesothelial lining of the peritoneum that was first described a century ago(1). There are approximately 400 new cases of MPM diagnosed annually in the United States with both males and females having an equal incidence of the disease(2;3). Grossly, MPM is characterized by innumerable tumor nodules of variable size diffusely located throughout the peritoneal cavity frequently resulting in massive malignant ascites; morbidity and mortality are almost always due to disease progression within the peritoneum. The diagnosis of MPM should be suspected in any individual with evidence of a diffuse malignant process in the abdomen on initial clinical evaluation and can be definitively established on the basis of diagnostic imaging with computed tomography (CT) scans and tissue biopsy with appropriate immunohistochemical staining (4). Historically, median overall survival for patients with MPM without treatment is about six months(5). Systemic chemotherapy using pemetrexed and cisplatin has an overall response rate of about 25% and a median overall survival of approximately one year(6).

Currently, operative cytoreduction (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) usually with mitomycin C or cisplatin has been established as the best initial therapeutic intervention in selected patients with MPM. Many institutional reports have shown that in patients with MPM operative cytoreduction and hyperthermic intraoperative peritoneal chemotherapy (HIPEC) using cisplatin or mitomycin-C is associated with long term survival. The overall median survival for patients following CRS and HIPEC ranges from 34.2 months to 92 months(7–10). A multi-institutional registry combining retrospective data on 405 patients with MPM treated with CRS and HIPEC at 29 centers worldwide reported a median actuarial overall survival of 53 months(11). On multivariate analysis prognostic factors that were independently associated with improved survival included epithelioid subtype, absence of lymph node metastases, complete or near complete cytoreduction (CCR-0 or CCR-1), and the use of HIPEC. Recent data from Wake Forest University that compared the outcomes of patients treated with mitomycin C versus cisplatin during HIPEC was interesting in that there was a trend for improved overall survival for patients perfused with cisplatin(12).

The current study is an analysis of 211 patients with high grade MPM treated at 3 major referral centers in the United States from 1992 to the present to identify parameters associated with outcome that may assist in patient selection and treatment in the future.

Patients and Methods

Patients

This study reviews data from 211 patients with histologically proven malignant peritoneal mesothelioma who underwent operative cytoreduction and hyperthermic intraoperative peritoneal perfusion (HIPEC) with chemotherapy between 1992 and 2011. Data review and analysis was conducted with the approval of the Institutional Review Boards of the three participating institutions (University of Maryland School of Medicine, Baltimore; University of Pittsburgh Medical Center, Pittsburgh; and the National Cancer Institute, Bethesda). All patients were assessed clinically as acceptable operative candidates with a disease burden judged to be amenable to a complete gross cytoreduction based on laparoscopic or radiographic findings. The first six authors practiced together in the Surgery Branch at the National Cancer Institute highlighting the fact that largely uniform criteria were employed at all institutions for patient selection, operative technique, HIPEC parameters, and follow-up protocols.

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Patients underwent exploratory laparotomy, lysis of adhesions, cytoreduction, and HIPEC as previously described(13). The goal of surgery was to render each patient grossly free of disease by systematically exploring all regions of the peritoneal cavity and addressing tumor implants via resection or thermal ablation while attempting to maintain normal digestive function and quality of life after the procedure. To that end procedures were designed to be visceral sparing, that is performed without an intestinal resection or a permanent end stoma if possible. For the parietal peritoneum, a peritoneal stripping was performed where disease was present but area where the peritoneum was normal appearing were not routinely removed. The pelvic peritoneum was removed without a rectal resection where possible; if a rectal resection was performed then a temporary diverting loop ileostomy was created. In post-menopausal women a hysterectomy and bilateral salpingo-oophorectomy were performed when indicated; in premenopausal women that procedure was performed selectively in an attempt to preserve organs. Omentectomy with or without splenectomy were almost always performed as omentum is a favored site for disease. The mesentery of the small bowel, liver capsule, and peritoneum over the pancreas were treated with local thermal ablation. Diffuse disease on the serosa of the small bowel represented an area of limitation with respect to resection or thermal ablation.

After cytoreduction, HIPEC was administered for 90 minutes using a closed recirculating system consisting of a reservoir, roller pump, and heat exchanger using either cisplatin or mitomycin C as previously described(13–15). These agents have been commonly used as they have demonstrated favorable pharmacokinetic profiles when administered via HIPEC(16)], they have a non-specific mechanism of anti-tumor activity, they do not have demonstrable toxicity to the normal peritoneal tissues, and they have synergistic actions with hyperthermia against cancer cells in experimental models(16;17;17). The morbidity and mortality from CRS and HIPEC has been described in numerous previous reports including from our own institutions; overall morbidity ranges from 25% to 50% and operative mortality is less than 2%(7;11;15). Thirty-five patients at the NCI also received a single dose of intraperitoneal paclitaxel and 5-fluorouracil in 35 patients on post-operative day 7 to 10(14). The perfusion flow rate was maintained at 1.5 L/min primarily to warm the peritoneal tissues using a perfusate volume that varied from 4 to 6 L depending on the size of the potential space of the peritoneal cavity (enough to distend the abdomen moderately). The peritoneal cavity was warmed to a median temperature of 41°C, and cisplatin at a median dose of 250 mg/m^2 or mitomycin C, 40 mg, was added to the perfusate. Perfusion was continued for 90 minutes, during which there was constant, manual agitation of the abdomen to minimize streaming and ensure even distribution of the perfusate. In patients receiving cisplatin, sodium thiosulfate was given around the time of HIPEC as previously described(13).

Initial and Follow-Up Evaluation

Before treatment, each patient underwent a full medical history, physical examination, routine laboratory studies, and a computed tomographic (CT) or magnetic resonance imaging (MRI) scan of the abdomen, and pelvis. Intraoperatively, the extent of residual disease or completeness of cytoreduction (CCR) after debulking was assessed as follows: CCR 0, no gross residual disease; CCR 1, fewer than 100 total lesions all smaller than 5 mm; CCR 2, more than 100 total lesions all less than 5 mm or any one greater than 5 mm; and CCR 3, residual tumor larger than 1 cm. Toxicity was assessed using the National Cancer Institute common toxicity criteria (version 2.0). Generally, patients were evaluated 3 to 6 weeks postoperatively and then every 3 months for 1 year, every 4 months for 1 year, and then every 6 months with blood work, physical examination, and CT of the chest, abdomen, and pelvis to assess for ascites or soft tissue masses indicative of tumor recurrence. No planned second-look operation was performed for assessment of response.

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Patients were considered to have stable disease until they had radiographic evidence of recurrence. Many patients went on to receive second or third line treatments at some point in their disease course.

Histologic Categorization of Tumors

Diagnosis of mesothelioma was confirmed in each patient, including review of pertinent immunohistochemical studies. Tumors were categorized histologically as adenomatoid, tubulopapillary, solid-epithelioid, or sarcomatoid. Adenomatoid and tubulopapillary tumors were grouped together as low grade, whereas solid-epithelioid and sarcomatoid tumors were grouped as high grade. When more than one histologic type was present the tumor was classified according to the highest grade type present.

Statistical Analysis

The primary objective of the analysis was to identify factors associated with progression-free survival (PFS) and overall survival (OS). For each end point, an actuarial analysis was initially performed, using the Kaplan-Meier method with two-tailed log-rank *P* values to evaluate potential prognostic variables. On the basis of the univariate analyses, a subset of variables was chosen to include in a Cox proportional hazards analysis to determine which, if any, variables were jointly important in prognosis. All *P* values were two-tailed.

Results

Approximately 60% of the 211 patients were female and the median age was 52 years; remarkably, the age range from youngest to oldest patient was almost 70 years (Table 1). Just under half of the patients were treated at the NCI and the number of patients treated with cisplatin versus mitomycin C was almost equal. Just over half of patients had a complete or near complete cytoreduction (CCR ≤ 1) consistent with our previous experience and that of others(10;11;16;17–19). The median actuarial overall survival was 38.4 months; the actuarial 5 and 10 year survivals were 41% and 26%, respectively (Figure 1).

A summary of the morbidity, mortality, and complications experienced in the patient cohort is shown in Table 2. Sixty-three of 211 patients (30%) had 1 or more complications and 20 of 211 patients had an unplanned return to the OR (9.4%). The operative mortality was 2.3% and the median length of stay was 11 days. The most common complications were intra-abdominal and included fistula, perforation, dehiscence, or infection in approximately 10%; prolonged ileus, vomiting, or obstruction in another 5%; and isolated surgical site infection in 4.4%. The second most common type of complications were non-infectious cardiopulmonary events and included pulmonary embolism, pleural effusion requiring intervention, or atrial fibrillation.

A number of patient, tumor, and treatment related factors were tested for any association with outcome. On univariate analysis male gender, age ≥ 60 years, high grade histology, CCR ≥2, and HIPEC agent (mitomycin C versus cisplatin) were found to be associated with worsened overall survival (Table 3). Multivariate analysis confirmed these parameters to be independently significant in predicting shortened survival (Table 4, Figures 2 and 3). We were interested in determining if choice of chemotherapy had any association on survival and observed that the use of cisplatin was associated with significantly prolonged survival compared to mitomycin C. It is interesting that this benefit was observed exclusively in patients who had an optimal, CCR≤1, cytoreduction (Figure 3). In patients with a suboptimal cytoreduction, CCR ≥ 2, outcome was poor and not influenced by choice of HIPEC agent (Figure 3).

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Discussion

These data confirm previous published reports that operative cytoreduction and HIPEC is associated with long term survival in selected patients with MPM(10;11;16;17–19). Because of the common institutional pedigree of the treating surgeons, we believe there was considerable uniformity in the criteria for selection, operative and HIPEC techniques, and follow-up protocols. Male gender, advanced age, high grade histology, and completeness of cytoreduction were all independent and significant factors associated with shortened survival consistent with reports of others.

The number of complications, types of complications, and operative mortality are consistent with contemporaneous reports of patients undergoing CRS and HIPEC for management of peritoneal metastases from appendiceal adenocarcinoma, colorectal cancer, or mesothelioma(15). The operative mortality of 2.3% reflects the improvements in patient selection, standardization of operative and HIPEC technique, and the post-operative management and is similar to the 2% operative mortality reported in a multi-center study of over 500 patients with MPM(11). We were unable to report specific complications for all 211 patients as one institutions recorded only severity of complications but not type. However, we feel that the reported types and frequency of complications in 135 patients reflected the realistic and accurate assessment of the spectrum of complications that might occur after this type of treatment.

The contribution of HIPEC to outcome following cytoreduction of peritoneal metastases from any histology has been the topic of considerable debate. There are no published data comparing patients who have undergone cytoreduction alone versus with HIPEC and/or early post-operative intraperitoneal chemotherapy (EPIC). Levine and colleagues from Wake Forest University published an analysis of factors associated with outcome in a small cohort of patients with MPM and showed a trend towards improved survival with cisplatin versus mitomycin C(2). Our data show a statistically significant difference in outcome based on the type of chemotherapy; this is the first documentation of a salutary effect of HIPEC in this patient population. The fact that the benefit was observed only in those who had an optimal cytoreduction supports the hypothesis that regional high dose chemotherapy administered via HIPEC has efficacy against minimal or microscopic residual disease in the peritoneum. Furthermore, the data do not support the use of HIPEC in patients who have suboptimal cytoreduction or extensive gross residual disease.

It is interesting to note that patients are at risk of death from disease for many years after initial treatment; the fact that the slope of the survival curve appears somewhat constant for over 8 years highlights the remarkable heterogeneity in the biological behavior of this condition. Also, even in patients who had an optimal cytoreduction (CCR<1) and HIPEC with cisplatin, the disease mortality is consistent with the overall group. There have been recent advances into the molecular features of MPM that provide insights into its biological behavior and have provided new potential molecular targets for therapeutic intervention. The epidermal growth factor receptor is over-expressed in the majority of MPM tumors and approximately 30% have activating mutations in the receptor(20). Phosphinositide-3-kinase (PI3K) and the mammalian target of rapamycin (mTOR) have recently been shown to be over-expressed in MPM and tumors with tumors with the highest expression of genes related to these cell signaling pathways are associated with significantly shortened patient survival(21). Specific inhibitors of these pathways have been shown to inhibit cellular proliferation and MPM xenograft growth in nude mice. Together, it is reasonable to anticipate that CRS and HIPEC may be offered in conjunction with specific and active molecularly targeted agents in the future. Currently clinical trials to test the efficacy of

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inhibitors against the epidermal growth factor receptor and PI3K are in clinical trials (H. Kindler, University of Chicago, personal communication).

In 1960 Winslow and Taylor provided the first detailed description of the pathological features of MPM in a collected series of 12 patients with MPM(22). In their review they wrote that “the value of making a diagnosis during life may be questionable, since at the present time there appears to be no cure. As time goes on, however, it may be that a cure will be developed and that such patients will not be considered definitely doomed…” Today, CRS and HIPEC represent what many would accept as the standard of care for selected patients with MPM and for which long term survival has been indisputably associated.

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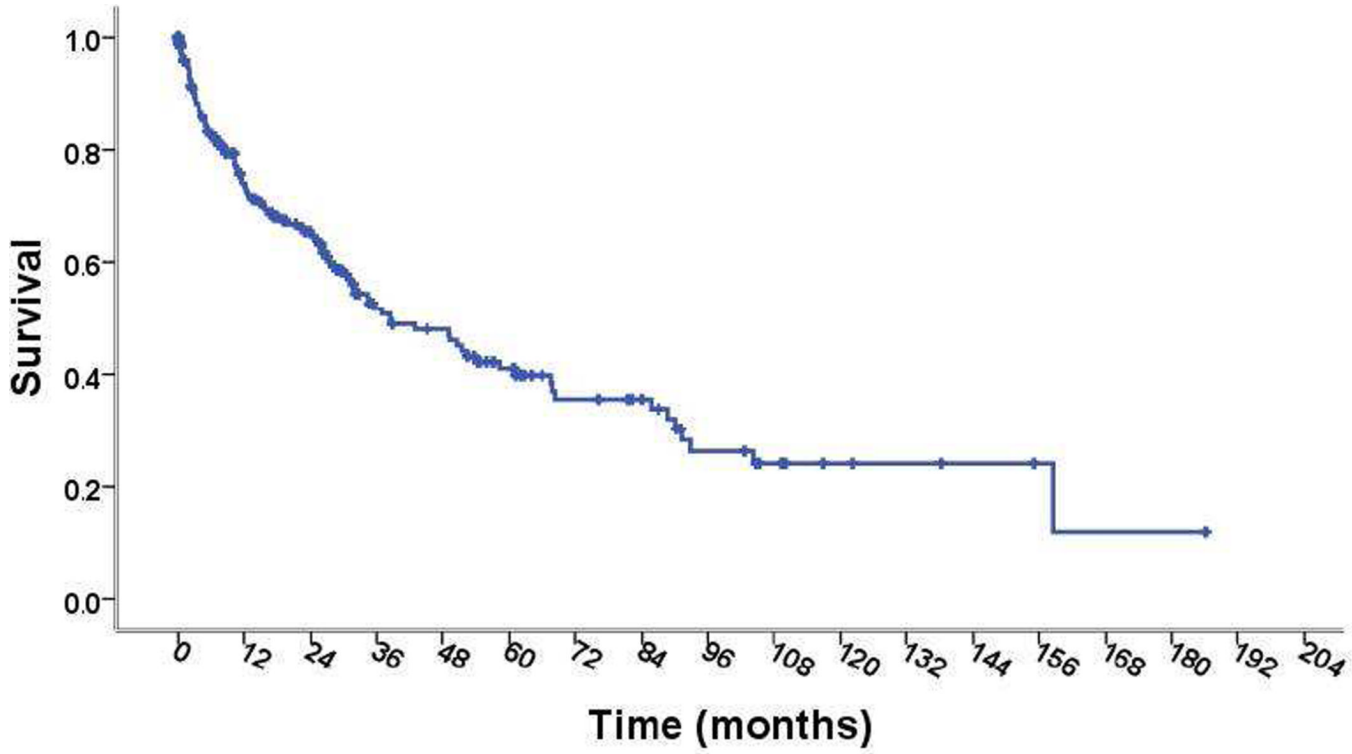

Figure 1.
Kaplan-Meier actuarial overall survival curve for all patients with MPM treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (n=211). The median actuarial overall survival was 38.4 months; the actuarial 5 and 10 year survivals were 41% and 26%, respectively.

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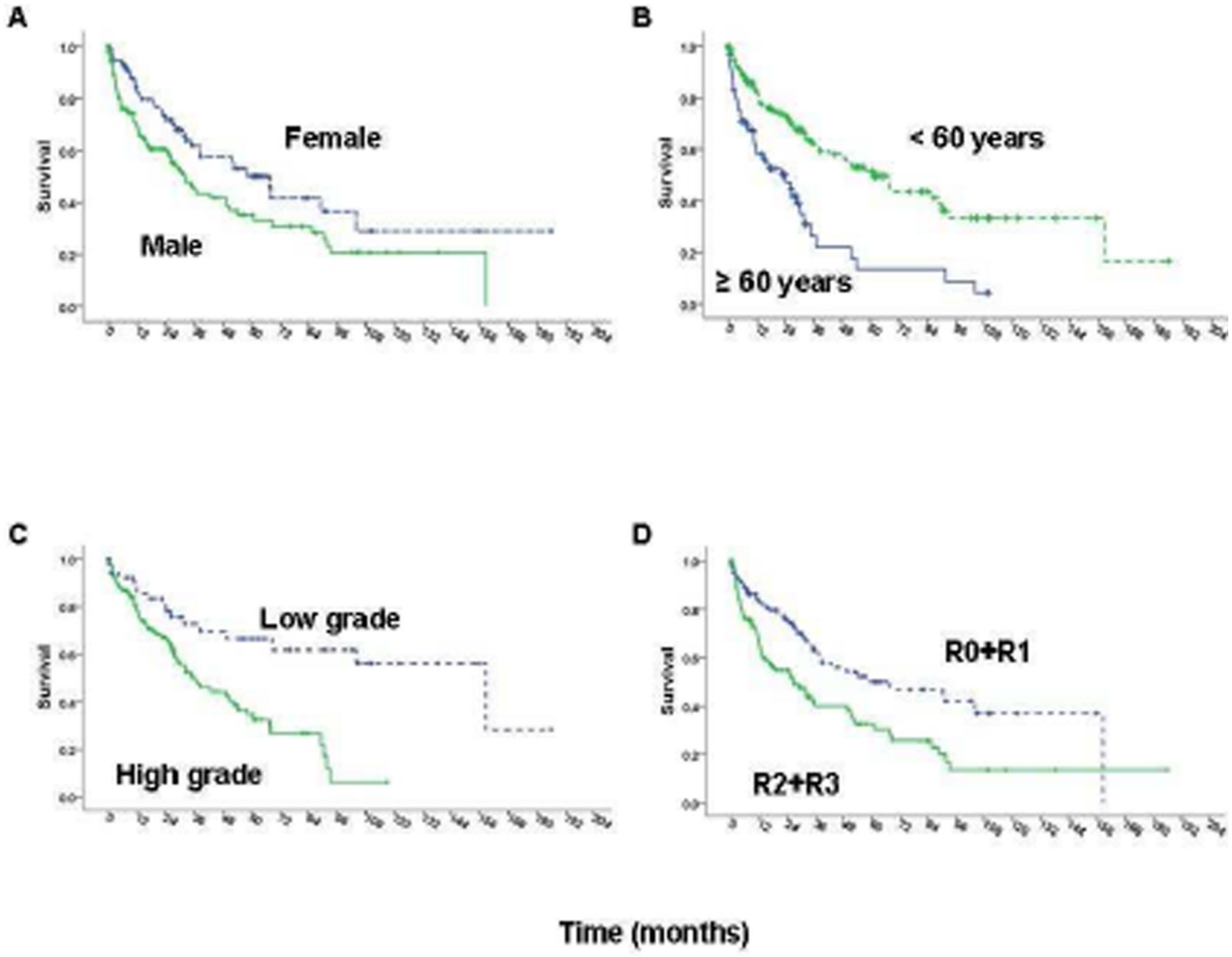

Figure 2.

Actuarial overall survival in patients with MPM was significantly shorter in male versus female patients (A), patients ≥ 60 years versus younger (B), patients with high versus low histologic grade tumors (C), and patients who had suboptimal (R2+R3) versus optimal (R0+R1) cytoreduction (D). All p-values are ≤ 0.02.

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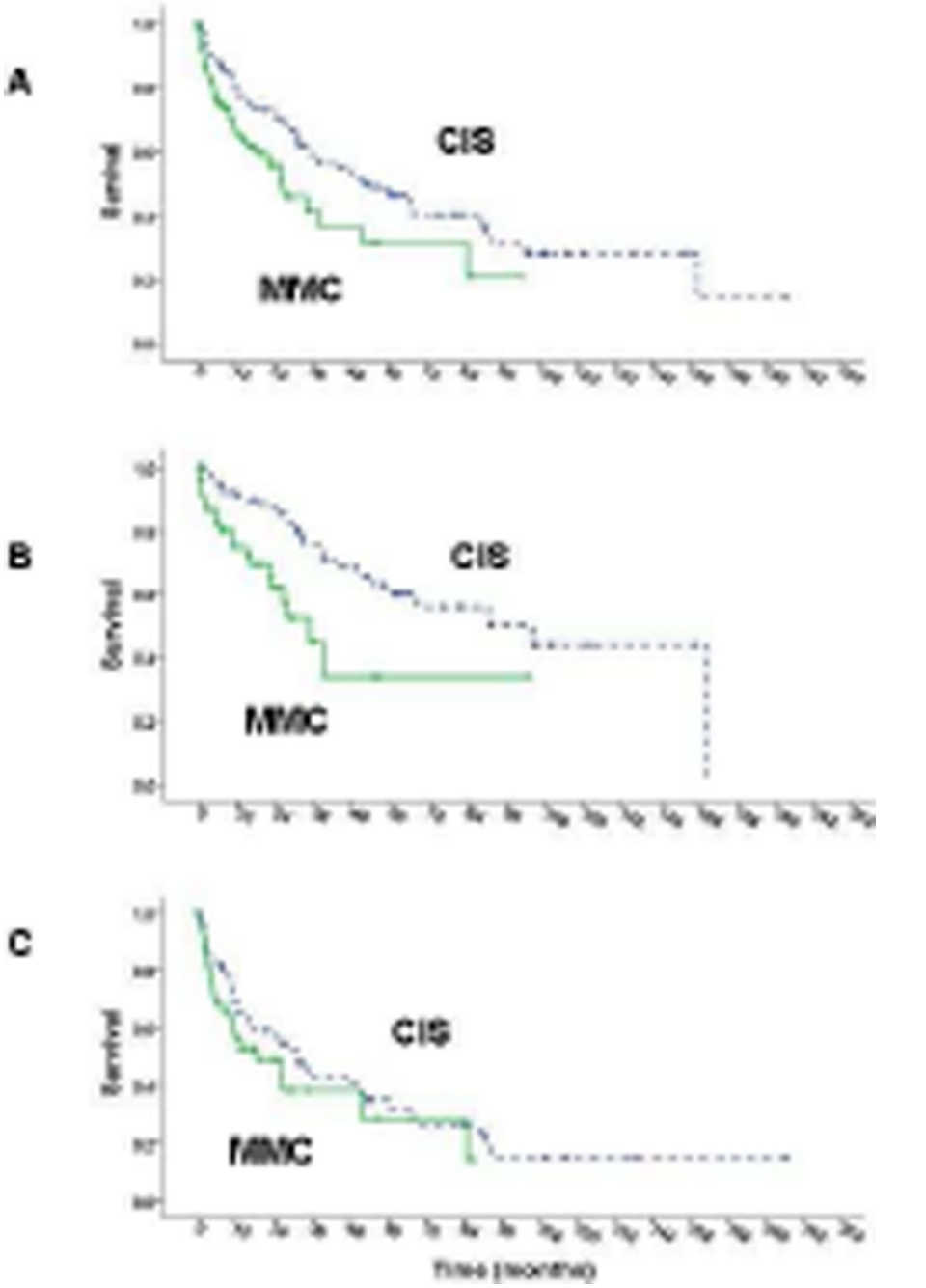

Figure 3.

Actuarial overall survival in patients with MPM based on cisplatin (CIS, n=105) versus mitomycin C (MMC, n=106) administration during HIPEC (A). Survival was significantly longer in patients who received cisplatin ($p \leq 0.01$). There was a significantly longer survival ($p \leq 0.02$) in patients treated with cisplatin versus mitomycin c who had an optimal cytoreduction (B); however, there was no difference in survival with mitomycin versus cisplatin in patients who had a suboptimal cytoreduction (C).

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Table 1

Demographics

	N=(211)	Percentage (%)
Gender		
Male	82	38.9
Female	129	61.1
Age	52	15.6–84.6
Histology Diagnosis		
High	113	53.5
Low	54	25.1
Unknown	44	21.4
Residual Disease		
R_0+R_1	111	52.6
R_2+R_3	100	47.4
Affiliation		
NCI	97	46.0
PIT	72	34.1
UM	42	19.9
Agents		
MMC	106	50.2
Dose	40mg	
Cisplatin	105	49.8
Dose	250mg	

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Table 2

Complications after CRS and HIPEC in 211 MPM Patients*

Patients with >1 complication	63/211 (30%)
Patients returned to OR	20/211 (9.4%)
Operative mortality	5/211 (2.3%)
Length of hospital stay (days; median, range)	11 (2–64)
Types of Complications	N (%)*
Intra-abdominal (fistula, perforation, dehiscence, infection)	13/135 (9.6%)
Surgical Site Infection	6/135 (4.4%)
Non-infectious cardio-pulmonary (pulmonary embolism, pleural effusion, atrial-fibrillation)	16/135 (12%)
Gastro-intestinal (ileus, vomiting, obstruction)	7/137 (5.2%)
Vascular (thrombosis, arterial injury)	4/135 (3%)
Hematologic	5/135 (3.7%)

* Severity but not types of complications were recorded at 1 institution and therefore types of complications can be tabulated for only two sites; complication rates were not different between institutions.

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Table 3

Univariate Analysis of Factors Potentially Associated with Outcome

	Hazard Ratio	95% CI	Standard Error	P-Value
Gender				
Male	1.64	1.08–2.49	0.21	0.02
Female	1			
Age				
>60 years	2.53	1.67 – 3.79	0.21	<0.01
<60 years	1			
Histology Diagnosis				
High	2.80	1.57 – 4.99	0.29	<0.01
Low	1			
Residual Disease				
R_2+R_3	1.89	1.27 – 2.82	0.20	<0.01
R_0+R_1	1			
Agents				
MMC	1.73	1.14 – 2.64	0.21	0.01
Cisplatin	1			

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Table 4

Multivariate Analysis of Factors Independently Associated with Outcome

	Hazard Ratio	95% CI	Standard Error	P-Value
Gender				
Male	1.46	0.89 – 2.41	0.26	0.13
Female	1			
Age				
>60 years	2.05	1.24 – 3.39	0.26	<0.01
<60 years	1			
Histology Diagnosis				
High	2.14	1.17 – 3.91	0.31	0.01
Low	1			
Residual Disease				
R_2+R_3	1.81	1.11 – 2.95	0.25	0.02
R_0+R_1	1			
Agents				
MMC	2.58	1.49 – 4.47	0.28	<0.01
Cisplatin	1			