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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Recurrence of Optimally Treated Malignant Peritoneal Mesothelioma with Cytoreduction and Heated Intraperitoneal Chemotherapy

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ABSTRACT

Background. The prognosis for patients with diffuse malignant peritoneal mesothelioma has dramatically improved with cytoreductive surgery and intraperitoneal chemotherapy. Little is known about disease recurrence after treatment. We analyzed the time to and predictors of recurrence in a large cohort of optimally treated patients.

Methods. We examined 113 patients completing a two-stage cytoreduction and intraperitoneal chemotherapy protocol. All patients achieved optimal surgical resection with completeness of cytoreduction (CC) score ≤ 1 and were divided into two groups based on absence (Group A) or presence (Group B) of gross disease at the outset of the second operation. Predictors of disease recurrence and recurrence-free survival (RFS) were determined using Cox proportional hazard regression modeling, and estimates were obtained by using the Kaplan–Meier method.

Results. Forty-six percent of patients had no gross evidence of disease at the second operation; the remaining 54% were cytoreduced to CC ≤ 1 (Group B). Forty-two percent of patients developed disease recurrence with a median recurrence-free survival of 38.5 months for the cohort; 79% of these received a form of iterative treatment. There was no statistically significant difference in recurrence-free survival between Group A (median RFS: 44.6 months) and B (median RFS: 35.5 months) (log-rank test, $p = 0.06$). Additionally, the only variable significantly associated with RFS was male gender (hazard ratio [HR] 1.98, 95% confidence interval [CI] 1.16–3.38).

Conclusions. Absence of gross disease at the second operation was not statistically protective against recurrence compared with presence of quantifiable residual disease (Group B) that was effectively cytoreduced. Long-term disease surveillance is recommended, because recurrence continues years after treatment. Where a question of recurrence arises on surveillance, males may benefit from a higher degree of suspicion.

Diffuse malignant peritoneal mesothelioma (DMPM) is a rare and fatal disease of the lining of the abdominal cavity. It represents approximately 20% of all mesothelioma cases, with pleural mesothelioma much more common.[1] In the United States, the incidence of DMPM is approximately 200–400 cases each year.[2] According to a recent report by the World Health Organization, mortality from DMPM has been growing by 2.78% each year from 1994 to 2008.[1,3]

Overall survival remains the primary endpoint of most DMPM investigations, stemming from an abysmal historical survival of 6–12 months. In the 1990s, Sugarbaker and associates demonstrated that treating DMPM with cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) dramatically improved median overall survival to 30–59 months.[4,5] This has been replicated, such that median survival is 38–53 months in the largest multi-institutional studies.[6,7] In 2010, Kluger and colleagues demonstrated that a staged

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operative approach was associated with relatively lower morbidity, mortality, and length of hospitalization than a single extensive CRS, with comparable median survival of 54.9 months.[8] Additionally, fewer visceral resections, complete peritonectomies, ostomies, chest tubes, standardized TPN, and routine intensive care unit stays were practiced.

DMPM disease recurrence is rarely investigated in the literature. The National Cancer Institutes in Milan and Bethesda reported progression-free survival of 9–14 months and 17–21 months, respectively, after CRS and HIPEC in large patient samples confined to malignant histologies.[9–12] Knowledge of rates and predictors of recurrence after CRS and HIPEC remains inadequate to inform surveillance practices and guide decisions about retreatment. The objective of the current study was to determine the time to and predictors of recurrence in a large cohort of patients with DMPM achieving CC $\leq$ 1 cytoreduction over two operative procedures and HIPEC. Routine second procedures allowed an assessment of therapeutic response and provided a baseline for time to recurrence.

METHODS

Patients selected for operative treatment had histologically proven epithelioid, sarcomatoid, or biphasic DMPM, surgically resectable disease on cross-sectional imaging, and a functional status and comorbidity profile appropriate for surgical intervention. Patients underwent treatment between 1995 and 2014 according to institutional protocol, which includes two CRS-HIPEC procedures with adjuvant dwell intraperitoneal chemotherapy. Surgical technique and HIPEC administration have been previously described.[8,13] In brief, patients underwent exploratory laparotomy through a midline incision. Bulky disease, defined as tumor nodules greater than 0.5 cm in depth or plaques greater than 0.5 cm in diameter—equivalent to a Lesion Size (LS) score of 2 or 3 as defined by the Peritoneal Carcinoma Index—was resected by peritonectomy, wedge, or en bloc excision. Two cannulae for the administration of HIPEC were inserted, and the skin was closed with a running suture. Mitomycin (10 mg/m^2) or Cisplatin (100 mg/m^2) were perfused at 42 °C for 60 min, and the patient's position was changed every 5 min. Two single-lumen peritoneal ports were inserted at the bilateral costal margins (Bard Access Systems: Salt Lake City, UT). Two to three weeks after surgery, weekly intraperitoneal infusions of Cisplatin alone (100 mg/m^2) or Cisplatin (50 mg/m^2) plus Gemcitabine (250 mg/m^2), alternating with a fixed-dose Doxorubicin (25 mg), were given for a total of eight cycles. After recovery from surgery and completion of intraperitoneal chemotherapy, a second exploratory laparotomy was performed. If no residual disease was identified, the peritoneal ports were removed, random four-quadrant biopsies were performed, and the patient underwent HIPEC. If tumor was present, cytoreduction with the objective of complete resection of all residual tumor of any size was performed, followed by HIPEC. Optimal cytoreduction was defined as achievement of CC $\leq$ 1 at the conclusion of the second operation with the administration of HIPEC. Only those who completed the two-stage protocol were included in this study. Patients with incomplete tumor debulking (CC $\geq$ 2) at the second CRS (n = 12) were considered suboptimally treated and were excluded from analyses.

Follow-up Disease Screening

Patients who completed the protocol were screened for disease recurrence every 6 months with CT of the chest, abdomen, and pelvis. PET studies were performed when surveillance CT showed evidence of disease progression. Recurrence was defined as new disease evidenced by both CT and confirmatory PET. Patients with recurrence were evaluated for iterative treatment eligibility based on disease burden and performance status. Retreatment consisted of further cytoreduction, HIPEC, and/or systemic chemotherapy based on a multidisciplinary decision among medical and surgical oncology teams.

Statistical Analysis

Patient care data was recorded prospectively in a database approved by the Institutional Review Board. The primary endpoint for this study was recurrence-free survival (RFS), defined as time from the date of the second CRS to the date of first detection of recurrence by cross-sectional imaging or death. Patients who did not recur and/or died were censored at the date of last contact. Secondary endpoints included overall survival (OS) defined as time from the date of second CRS to death or last follow-up. Patients were divided into two groups based on clinical disease status at the second exploration: no gross disease (Group A) and gross disease requiring CRS (Group B). Gross disease was defined as mesothelioma nodules visible to the naked eye on second exploration.

Recurrence-free and overall survival were estimated using the Kaplan–Meier method. Continuous variables, reported as median and interquartile range (IQR), were compared between the two groups using the nonparametric Wilcoxon rank-sum tests. Categorical variables were summarized as frequency and percentages and compared using Pearson's Chi squared or Fisher's exact tests. Univariable and multivariable Cox regression

models were employed to identify clinical/pathologic factors associated with recurrence-free survival. The Cox proportionality assumption was tested for each of the variables considered in the model by including an interaction of that variable with the natural logarithm of time. There were no indications of proportionality violation. All variables with a $p < 0.15$ in univariable analyses were further tested in the multivariable model; $p < 0.05$ was considered statistically significant. The overall C-index of concordance was used as a measure of discrimination for validating the multivariable recurrence model.[14,15] Outcomes were not affected when a competing risk model was used; determination was there were too few competing events. All analyses were performed using Stata 11 (StataCorp, College Station, TX).

RESULTS

A total of 113 individuals completed the treatment protocol with CC $\leq$ 1 resections, of which 57 (50%) were male and 94 (83%) were Caucasian, with a median age of 53 (IQR 42–62). Epithelioid disease was predominant; only nine patients (8%) had sarcomatoid or biphasic histology. Twenty-four patients (21%) had both pleural and peritoneal mesothelioma; 14 (12%) developed pleural disease after completing treatment for peritoneal disease (Table 1).

Operative Details: First Stage

Peritoneal Cancer Index (PCI) data were available for 45 of 113 patients at the first operation, because the institution did not record this index until 2010. Median PCI at the first stage was 15 (IQR 10–21). Forty-three patients (38%) had bulky disease (LS 2 or LS 3). Because HIPEC was not administered at the first CRS before 2005, 66 (58%) patients received HIPEC at the first stage (Table 1). All patients received extended dwell chemotherapy postoperatively, with 28% additionally treated with abdominal radiation and 20% treated with gamma interferon during Phase I and II trials.[8,13]

Operative Details: Second Stage

The second stage procedure took place at a median of 5.4 (IQR 4.8–5.9) months after the first procedure. The median PCI at the second operation was 2 (IQR 0–5) for 49 patients. Sixteen patients (14%) had bulky disease (LS 2 or LS 3) at laparotomy. Forty-six percent of patients had no gross disease (Group A), and 54% had a complete cytoreduction of gross disease to CC $\leq$ 1 (Group B). HIPEC was administered to 105 (93%) patients (Table 1).

Recurrence

Forty-seven patients (42%) developed evidence of recurrence on routine surveillance imaging.

Of these patients, 15 (32%) received both cytoreductive surgery and systemic chemotherapy, 14 (30%) received CRS only, 8 (17%) received systemic chemotherapy only, and 10 (21%) received no therapy. Of those undergoing repeat CRS, 15 (52%) received HIPEC.

Of the 47 patients who recurred, 23 patients were from Group A and 24 from Group B ($p = 0.086$). The overall median recurrence-free survival after the second stage procedure was 38.5 months (95% CI 29.5–54), with a median recurrence follow-up time of 25.8 months. Median recurrence-free survival was 44.6 months (95% CI 29–136) for Group A and 35.5 months (95% CI 23.8–48.1) for Group B (Fig. 1). However, further testing showed no statistical significant difference between the recurrence-free survivals of the two groups (log-rank test, $p = 0.06$). For the entire cohort, 1-, 5-, and 10-year recurrence-free survival probabilities were 79% (95% CI: 72-87), 37% (95% CI 27–46), and 29% (95% CI 19–39), respectively (Fig. 1).

On univariable analyses (Table 2), predictors of recurrence ($p < 0.15$) were included in the multivariable analyses. None of these variables remained significant ($p < 0.05$) with the exception of male gender (HR 1.98; 95% CI 1.16–3.38). Nonetheless, the multivariable survival model presented in Table 2 showed a fair predictive ability with a C-index of 0.73 (95% CI 0.52–0.91). Notably, absence of gross disease at the second operation (Group A) was not statistically protective against recurrence compared with presence of quantifiable residual disease (Group B) that was effectively cytoreduced. Bulky disease and PCI for the first and second operations were used in the model, because there was changeability over the operations. For example, 62 (55%) neither had bulky disease at the first or second operation, 35 (31%) had bulky disease only at the first operation, 8 (7%) had bulky disease only at the second operation, and 8 (7%) had bulky disease at both operations. Furthermore, these variables are indicators of tumor behavior and treatment response.

Survival

Median overall survival (OS) for all 113 patients from completion of treatment at second operation was 6.65 (95% CI 5.03–14.41) years, with a median survival follow-up time of 35.1 months. For patients completing the protocol, there was a significant difference in the overall survival based on disease burden at the outset of the second operation (log-rank test, $p = 0.028$; Fig. 2). Median overall survival was not reached for Group A and was 5.03 years

TABLE 1 Demographic and treatment details of 113 patients completing the protocol

	Total $N = 113$	No disease $n = 52$	Gross disease $n = 61$	p Value[b]
Male	57 (50)	32 (62)	25 (41)	0.029
Age, median (IQR)	53 (42,62)	53 (42,64)	54 (42,61)	0.758
Caucasian	94 (83)	44 (85)	50 (82)	0.605
ASA > 2	19 (17)	7 (14)	12 (20)	0.379
Pleural mesothelioma	24 (21)	8 (15)	16 (26)	0.160
First operation details				
PCI, median (IQR)	15 (10,21)	14 (4,20)	15 (12,23)	0.228
	$n = 45$	$n = 18$	$n = 27$	
Bulky disease[a]	43 (38)	14 (27)	29 (48)	0.024
HIPEC	66 (58)	32 (62)	34 (56)	0.533
Pathology				
Epithelioid	104 (92)	48 (92)	56 (92)	
Sarcomatoid/biphasic	9 (8)	4 (8)	5 (8)	0.921
Second operation details				
PCI, median (IQR)	2 (0.5)	0 (0.0)	5 (3,7)	0.001
	$n = 49$	$n = 22$	$n = 27$	
Bulky disease[a]	16 (14)	0	16 (26)	0.001
HIPEC	105 (93)	47 (90)	58 (95)	0.332
Peritoneal recurrence	47 (42)	23 (44)	24 (39)	0.599
Treatment of recurrence				
None	10 (21)	5 (22)	5 (21)	
Chemotherapy	8 (17)	6 (26)	2 (8)	
Cytoreductive surgery	14 (30)	5 (22)	9 (38)	
Chemotherapy and surgery	15 (32)	7 (30)	8 (33)	0.363
Final status				0.092
Dead	47 (42)	16 (31)	31 (51)	
Alive with disease	19 (17)	11 (21)	8 (13)	
Alive without disease	47 (42)	25 (48)	22 (36)	

All summary statistics are shown as n (%) unless specified otherwise

[a] Bulky disease is equivalent to tumor burden > LS 1 as defined by the Peritoneal Carcinoma Index

[b] p Values generated by Wilcoxon rank-sum test or Chi squared/Fisher's exact test

ASA American Society of Anesthesiologists' Classification; *PCI* peritoneal carcinoma index, *HIPEC* hyperthermic intraperitoneal chemotherapy

(95% CI 3.82–10.1) for Group B. Of note, the 12 patients not undergoing complete cytoreduction at the second operation who were excluded from the recurrence analyses had a median overall survival of 22.9 months (95% CI 0.87–NA).

DISCUSSION

Patient survival after CRS and HIPEC to treat DMPM has dramatically improved during the past two decades.[6,7,16] Recent studies have focused on repeat CRS and HIPEC in select patients with recurrent disease, previously an inconceivable prospect.[9,17–19] These studies describe reoperating on 22–46% of patients but do not report the rates of recurrence. The rate of recurrence has not been well-studied in large samples of patients with malignant peritoneal mesothelioma histopathology. To further guide long-term management, this study investigated clinical recurrence after CC $\leq$ 1 CRS/HIPEC in a large group of DMPM patients.

We found that after optimal CRS and HIPEC, recurrent disease identified by cross-sectional contrast-enhanced imaging occurred at a median of 38.5 months. This is remarkable given that survival of patients with untreated disease has historically been reported as less than 1 year. As with most malignancies, recurrences concentrated early

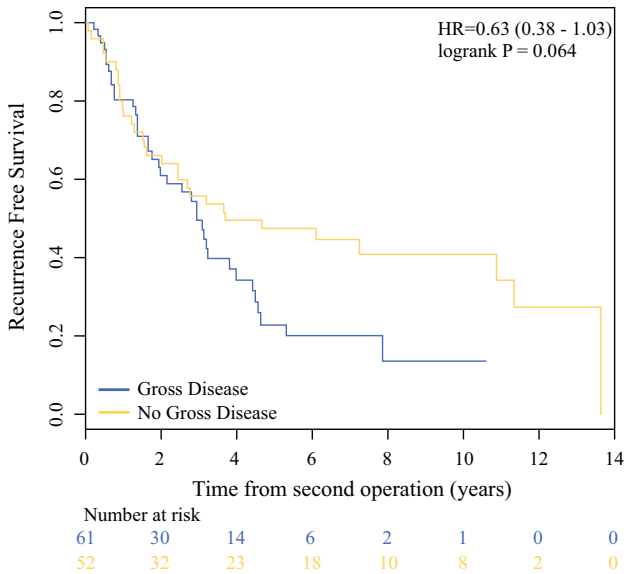

FIG. 1 Kaplan-Meier recurrence-free survival estimates for patients with diffuse malignant peritoneal mesothelioma optimally treated with cytoreduction (CC ≤ 1) and intraperitoneal chemotherapy. Gross disease visualized at outset of second operation. No gross disease visualized at outset of second operation. Time zero defined as date of second operation

during the surveillance period and slowed with time. At 10 years, though, 29% of patients remained alive without recurrence.

Although there was an accelerated recurrence rate among patients with gross disease at the outset of the second operation compared with those with no gross disease, this difference was not significant. This may be explained by the effective cytoreduction to CC ≤ 1 performed in both groups by the conclusion of the second CRS-HIPEC. Because 93% of patients received HIPEC at the second operation, we did not attempt to compare patient outcomes based on HIPEC versus no HIPEC. As such, this study continues to support maximum cytoreduction to less than 0.25 cm diameter disease (CC ≤ 1) followed by intraperitoneal chemotherapy as optimal treatment for DMPM.

Only male gender showed a statistically significant independent association with recurrence-free survival. Past studies have found other prognosticators related to overall survival, including peritoneal carcinoma index, advanced age, completeness of cytoreduction, histology, nodal status, and absence of HIPEC. In this study, due to the limited number of patients with documented PCI, we could not investigate its impact on recurrence. However, in the largest multi-institutional study of cytoreduction and HIPEC for DMPM, PCI was not shown to be a significant prognosticator on multivariable analyses.[7] It is interesting that histology did not predict recurrence, given that sarcomatoid and biphasic disease are more aggressive entities. Despite this finding, we do not advocate for

TABLE 2 Cox regression analysis for recurrence-free survival (RFS)

Variable	Univariable analysis		Multivariable analysis[b]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Disease status at 2nd operation				
No disease (A)	0.63 (0.38, 1.03)	0.066	0.89 (0.50, 1.57)	0.674
Gross disease (B)	Ref		Ref	
Demographics				
Sex (male)	2.14 (1.34, 3.41)	0.001	1.95 (1.16, 3.38)	0.013
Age (> 50)	1.34 (0.85, 2.13)	0.211	–	–
ASA (> 2)	1.08 (0.61, 1.93)	0.797	–	–
Pleural mesothelioma	1.68 (0.95, 2.63)	0.082	1.53 (0.87, 2.67)	0.137
First operation				
PCI (> 20)	1.63 (0.75, 3.58)	0.221	–	–
Bulky disease[a]	1.91 (1.20, 3.05)	0.007	1.56 (0.94, 2.60)	0.084
No HIPEC	0.95 (0.60, 1.50)	0.813	–	–
Sarcomatoid/biphasic	1.76 (0.84, 3.68)	0.132	1.51 (0.65, 3.55)	0.339
Second operation				
PCI (> 20)	1.57 (0.21, 11.8)	0.660	–	–
Bulky disease[a]	1.64 (0.96, 2.80)	0.069	1.05 (0.51, 2.19)	0.889
No HIPEC	1.34 (0.67, 2.69)	0.416	–	–

[a] Bulky disease is equivalent to tumor burden > LS 1 as defined by the Peritoneal Carcinoma Index

[b] Variables with *p* value < 0.15 were entered in the multivariable analysis

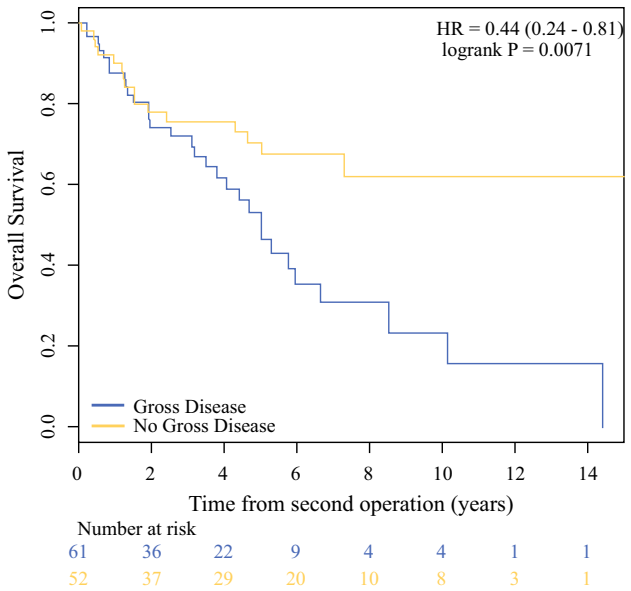

FIG. 2 Kaplan-Meier overall survival estimates for patients with diffuse malignant peritoneal mesothelioma optimally treated with cytoreduction (CC ≤ 1) and intraperitoneal chemotherapy. Gross disease visualized at outset of second operation. No gross disease visualized at outset of second operation. Time zero defined as date of second operation

extensive CRS-HIPEC treatment of patients with aggressive histologies and recognize our nine patients as exceptions. Still, this finding highlights the idea that the natural progression from mutated peritoneal mesothelial cell to identifiable mass is not well-understood and that herein unstudied or unidentified histological factors may influence recurrence. In the future, we intend to reexamine specimens to quantify mitotic index and p16 mutations, among other histologic factors, and assess their influence on recurrence.[20,21]

A strength of the current study comes from the second stage procedure. After initial cytoreduction of bulky disease (> LS-1), HIPEC in 58% of cases and dwell chemotherapy in 100%, direct observation of the treated abdomen occurred in 125 patients. Whereas completeness of cytoreduction relies on qualitative visual scoring at the completion of surgery, histopathology at the start of the second-stage operation demonstrated the impact of the current treatment protocol. Of the 52 patients (Group A) that had no gross evidence of disease, more than half (56%) had no microscopic disease on random four quadrant biopsy either. This supports the use of HIPEC and dwell chemotherapy to treat DMPM, because no effort is made at the first operation to extirpate visible disease < 0.5 cm. Our center has long argued that a two-stage operative protocol limits the extent of organ resections and complex peritoneal procedures required, based on the favorable response of DMPM to intraperitoneal chemotherapy.

The median overall survival estimate of this cohort of optimally treated patients with CC ≤ 1 CRS/HIPEC was 6.65 years. This has two important implications. First, long-term surveillance should be maintained, because recurrence can occur over an extended period. At 5 years, a point where many cancers are considered cured, nearly 50% of patients without gross disease at the outset of the second operation had recurred. Clinical recurrences observed in this cohort suggest a slow-growing disease process. Second, patients who recur can have a substantial survival and may be offered iterative treatments. Other studies have previously demonstrated that repeat surgical treatment in carefully selected patients is feasible, has acceptable morbidity and mortality, and can lead to disease remission with a possibility of prolonged survival.[9,17–19] In 2013, Wong and colleagues reported a statistically significant difference in median overall survival of patients who underwent primary cytoreduction (27.2 months) and patients who underwent iterative cytoreduction for recurrence (80 months), with no significant difference in morbidity or mortality between the two operations.[18] In 2014, Sugarbaker's group reported a median overall survival of 77 months for patients treated with single therapy compared with an additional 54 months from the time of iterative treatment for those with treated recurrences, also finding no difference in morbidity or mortality between the groups.[19] In the current series, 79% of patients who recurred received medical and/or operative treatment. In the absence of strong predictors of recurrence, centers should monitor all patients closely and make decisions about iterative therapies on a case-by-case basis.

The limitations of this study primarily relate to variations in treatment methods among patients in the early and late periods of our practice. Specifically, early in our experience, HIPEC was not administered during the first cytoreduction, and gamma interferon and/or abdominal radiation were administered to a portion of patients. After Phase I and II trials, HIPEC became standard at both operations, whereas interferon and radiation were stopped. Although the current treatment protocol differs from other widely used strategies, we believe that these findings may be applicable to CRS and HIPEC protocols effecting CC ≤ 1 resection. However, these data cannot be generalized to resected DMPM patients who do not achieve CC ≤ 1 cytoreduction. Because the objective of this paper was to study recurrence in optimally treated patients, 12 patients with incomplete debulking (CC ≥ 2) at the second CRS were excluded from the analyses. Inclusion of similar incompletely cytoreduced patients in time-to-progression analyses published by the Milan and Bethesda National Cancer Institutes may explain the differences in rates between those studies and ours.[9–12] For example, Baratti and colleagues elegantly reported disease progression in

more than 50% of patients at a median of 9 months from treatment, but at least 20% had CC > 1 cytoreduction.

CONCLUSIONS

In DMPM, recurrence-free survival does not significantly vary based on preoperative disease burden when complete operative cytoreduction is possible. All patients adequately treated for DMPM should undergo routine surveillance imaging indefinitely based on late recurrence years after complete operative cytoreduction. Males may benefit from a higher degree of suspicion during surveillance. Information provided by this study design may benefit both oncologists and patients by guiding expectations of recurrence and prognosis after successful treatment.

DISCLOSURES None.

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