

## Lymph Node Metastases in Diffuse Malignant Peritoneal Mesothelioma

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### ABSTRACT

**Background.** Improved survival has been reported for diffuse malignant peritoneal mesothelioma (DMPM) treated by surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). The significance of lymph node involvement in this disease is still poorly understood.

**Methods.** Prospectively collected clinical data on 83 consecutive patients with DMPM undergoing surgical cytoreduction and closed-abdomen HIPEC with cisplatin and doxorubicin were reviewed. Clinically suspicious lymph nodes were submitted to pathological examination. The impact of nodal involvement on survival was assessed by multivariate analysis; 14 clinicopathological control variables were tested.

**Results.** For the overall series, median follow-up was 52 months (range 1–126 months) and 5-year overall survival (OS) was 49.5%. Lymph nodes were submitted to pathological examination in 38 patients, being positive in 11 and negative in 27. Lymph nodes were not clinically suspicious and not sampled in 45 patients. Iliac ( $n = 7$ ) and paracolic ( $n = 2$ ) nodes were the most commonly involved nodes. OS was 18.0% for patients with pathologically positive nodes and 82.5% for those with pathologically negative nodes ( $P = 0.0024$ ). On multivariate analysis, pathologically negative (versus positive/not assessed) nodes [hazard ratio (HR) = 2.81; 95% confidence interval (CI) = 1.12–7.05;  $P = 0.027$ ], epithelial subtype (HR = 2.93; CI = 1.24–6.95;  $P = 0.015$ ), mitotic count  $\leq 5/50$  high-power microscopic fields (HPF) (HR = 5.34; CI = 1.96–14.54;  $P = 0.001$ ), and completeness of

cytoreduction (HR = 2.06; CI = 1.19–3.56;  $P = 0.001$ ) correlated with increased OS. Positive nodes (versus negative/not assessed) did not significantly correlate with survival.

**Conclusion.** Pathologically negative nodes (as compared with pathological positive and not assessed), along with pathological and biological features, independently correlated with increased survival following comprehensive treatment. This suggests the need for careful node sampling when performing surgical cytoreduction for DMPM patients.

Diffuse malignant peritoneal mesothelioma (DMPM) is a rare and rapidly fatal malignancy, unless special treatments are performed. In historical case series, standard therapy with palliative surgery and systemic or intraperitoneal chemotherapy is associated with median survival of about 12 months.<sup>1–3</sup>

In recent years, an aggressive multimodality approach has become a treatment option with curative intent for selected patients with DMPM. It involves peritonectomy procedures and multivisceral resections to remove all visible tumor, and perioperative intraperitoneal chemotherapy to treat microscopic residual disease. This comprehensive treatment has reportedly resulted in median survival of 34–92 months, strongly suggesting improved outcome and even the possibility of definitive cure.<sup>4–11</sup> Nevertheless, optimal adaptation of this treatment strategy is still a matter of clinical investigations, and the histological and molecular features associated with outcome have been extensively studied only in recent years.<sup>12,13</sup> Furthermore, no tumor–node–metastasis (TNM) classification or any other reliable staging system is currently available to help predict survival and select treatment options for these patients.

Lymph node metastases within and outside the abdominal cavity can occur even as the initial manifestation of DMPM, but their significance is still poorly understood.<sup>14</sup> The correlation between nodal status and survival was demonstrated in a series from the Washington Cancer Institute.<sup>15</sup> However, in other studies it was not clear if node metastases are independent or only minor prognostic factors.<sup>9,11,13</sup> Involvement of appendiceal or ileocolic lymph nodes does not correlate with survival in patients with pseudomyxoma peritonei, and the role of systematic lymphadenectomy in disseminated ovarian cancer is still controversial.<sup>16,17</sup>

The objective of the present study was to analyze a prospective database to address lymph node status and prognostic significance in patients affected by DMPM treated by surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC).

## PATIENTS AND METHODS

All the patients included in the present study were treated according to a protocol approved by the Institutional Ethics Committee and signed a written informed consent form. Data for the present analysis were collected from a prospective database. Additional information was retrieved from medical charts.

From January 1996 to December 2008, 83 consecutive patients with DMPM were treated with cytoreduction and HIPEC by the same surgical team at the National Cancer Institute, Milan, Italy. Patients with multicystic or papillary well-differentiated mesothelioma were excluded, as they represent different biological disease entities. Two patients with peritoneal spread from primary pleural mesothelioma were also excluded. Some of these patients were reported previously.<sup>8,18</sup>

### *Operative Treatment*

Diagnosis of DMPM was made or confirmed in our Pathology Department according to a previously described protocol including hematoxylin–eosin-stained sections and immunohistochemistry studies (calretinin, cytokeratins5/6, WT-1 antigen, polyclonal CEA, B72.3, Ber-Ep4).<sup>18</sup> Additional selection criteria included: age  $\leq 75$  years, performance status  $\leq 2$  according to Eastern Cooperative Oncology Group (ECOG) score, no significant comorbidities, no extra-abdominal or hepatic metastases, and peritoneal disease amenable to potentially complete surgical cytoreduction at preoperative computed tomography (CT) scan.<sup>19,20</sup>

The operative technique adopted in our center has been described previously.<sup>8</sup> Briefly, the goal of the surgical

cytoreduction was to remove all visible tumor by means of diaphragmatic, parietal anterior, and pelvic peritonectomy with greater and lesser omentectomy. Depending on disease involvement, multivisceral resections were performed, including cholecystectomy, splenectomy, sigmoid, right or total colectomy, and hysterectomy with salpingoophorectomy in women.

HIPEC was performed according to the closed-abdomen technique for 90 min, at temperature of 42.5°C, with cisplatin (45 ml/l) plus doxorubicin (15 mg/l).<sup>21</sup> Perfusate volume was 4–6 l, and average flow was 700 ml/min. The first ten patients of the series were treated with cisplatin (25 ml/m<sup>2</sup>/l) plus mitomycin-C (3.3 mg/m<sup>2</sup>/l). The Performer LRT<sup>®</sup> [RAND, Medolla (MO), Italy] extracorporeal circulation device was used.

The peritoneal cancer index (PCI) was used to score the extent of peritoneal involvement at surgical exploration.<sup>22</sup> All resected specimens were submitted to pathological examination. Completeness of cytoreduction (CC) was classified at the end of the surgical phase according to Sugarbaker criteria as: macroscopically complete cytoreduction (CC-0); nearly complete cytoreduction: residual disease  $\leq 2.5$  mm in any region (CC-1); or suboptimal cytoreduction: residual disease  $> 2.5$  mm (CC-2) or  $> 25$  mm (CC-3).<sup>23</sup> Postoperative complications occurring within 30 days of the procedure were scored according to the National Cancer Institute *Common Terminology Criteria for Adverse Events* version 3.0 (<http://ctep.cancer.gov/forms/CTCAEv3.pdf>). Tumors were histologically categorized as epithelial, biphasic or sarcomatoid, following the World Health Organization (WHO) classification.<sup>24</sup> Mitotic count per 50 high-power microscopic fields (HPF) was assessed.<sup>18</sup>

All patients underwent postoperative follow-up. Physical examination, thoracic/abdominal CT scan, and CA125 measurements were performed every 3 months during the first 2 years and every 6 months thereafter. Postoperative disease progression was confirmed at surgical exploration or by CT scan/ultrasound-guided biopsy. Alternatively, it was defined according to the Response Evaluation Criteria in Solid Tumor Group (RECIST).<sup>25</sup>

### *Lymph Node Assessment*

Intra-abdominal lymph nodes, including inguinal nodes, were considered local-regional nodes; nodal involvement beyond abdominal boundaries was considered distant metastasis. During the cytoreductive surgical procedures, enlarged or firm lymph nodes were excised and sent for pathological assessment separately. Tumor nodules were interpreted as metastatic lymph nodes if they were removed from anatomic sites containing nodes and some residual lymphoid tissue was present.

Pathology reports documented lymph node status in 38 patients (45.8%). Intraoperatively, lymph nodes were deemed clinically suspicious and submitted to pathological examination in 20 patients. Nodes were assessed by pathologists during routine examination in three patients. In the last 15 patients of the present series, bilateral iliac and ileocolic nodes were routinely sampled, as well as any other suspicious node seen in any other region. A median of 2 regions (mean 2.1; range 1–6) and of 6.5 lymph nodes (mean 8.94; range 1–52) were sampled. In the remaining 45 patients no lymph nodes were sampled or thought to be suspicious for metastatic disease.

### Statistics

The study end-point was survival. Lymph node status was the main independent variable considered. Since lymph nodes were deemed clinically negative and not assessed by pathology in a considerable number of patients, nodal status was categorized for the survival analysis in two different ways: (1) pathologically positive versus negative/not assessed, and (2) pathologically negative versus positive/not assessed. The following variables, chosen on the basis of literature information, were considered as control variables: age, sex, ECOG performance status, extent of surgery before referral, preoperative systemic chemotherapy, interval between diagnosis and combined treatment, histological variant, mitotic count, PCI, CC score, number of cytoreductive surgical procedures, HIPEC drug schedule (cisplatin and mitomycin-C versus cisplatin and doxorubicin), cisplatin dosage, and preoperative serum CA125. Continuous variables were categorized into two classes using their mean value as cutoff. Overall survival (OS) was calculated from the day of cytoreduction and HIPEC to the time of death due to any cause. Patients with uneventful postoperative course were censored at the time of last follow-up visit. OS was calculated according to the Kaplan–Meier method.<sup>26</sup> The two-tailed log-rank test was used to assess the significance of the comparison between survival distributions. Operative mortality was included in the survival statistical analysis. Multivariate analysis was performed by the Cox proportional hazard model using the backward-elimination method.<sup>27</sup> Variables deemed statistically significant on univariate analysis or considered clinically or theoretically relevant for the purpose of the study, regardless of their statistical significance, were included in the model. The Fisher's exact test and Mann–Whitney *U*-test were used to assess the distribution of nominal or continuous variables, as appropriate. *P*-values < 0.05 were considered significant. All statistical analyses were conducted by using SPSS software version 8.0.0 (SPSS Inc., Chicago, IL) for Windows.

## RESULTS

Patient characteristics according to lymph node status are shown in Table 1. In the overall series, median follow-up was 52 months (range 1–126 months). Median survival was 44 months; 5- and 10-year overall survival were 49.5 and 45.5%, respectively. Operative mortality occurred in 2 patients (2.4%) and grade 3–5 surgical complications in 23 patients (27.7%).

### Lymph Node Involvement

Regional lymph nodes were pathologically positive in 11 patients, accounting for 13.2% of the overall series and 28.9% of those who had their nodes submitted to pathological examination. Eight cases of positive lymph nodes were from the group of 20 patients whose nodes were thought to be suspicious and submitted to pathological examination (40%), and 3 were from the group of 15 patients whose nodes were routinely sampled (20%). Nodes were pathologically negative in 27 patients. Pathologically negative nodes were statistically associated with younger age and lower PCI, as compared with the subset of either pathologically positive or not assessed nodes. Patients with pathologically positive nodes showed a trend toward significance only for higher PCI, as compared with those with pathologically negative nodes (Table 1).

Internal, external, and common iliac lymph nodes were the most commonly involved nodes, being metastatic in seven patients; in detail, right, left, and bilateral iliac nodes were involved in four, one, and two patients, respectively. Five patients had metastatic iliac nodes only, one also had positive gastrohepatic ligament nodes, and one had positive bilateral iliac, epigastric, left inguinal, paracaval, and para-aortic nodes, with 21 positive of 52 examined nodes. Two patients had metastatic ileocolic and mesenteric nodes, respectively. The median number of metastatic lymph nodes per patient was 1 (mean 3.54; range 1–21). Table 2 details the number of both sampled and positive anatomic sites and lymph nodes.

### Survival by Lymph Node Status

Five-year overall survival was 82.5% for patients with pathologically negative nodes (median not reached), as compared with 16.7% (median 22 months) for those with pathologically positive nodes (*P* = 0.001) and 40.9% (median 26 months) for those with not assessed nodes (*P* = 0.009); the survival difference between patients with pathologically positive nodes and those with nodes not submitted to pathological examination was not statistically significant (*P* = 0.331) (Fig. 1). On univariate analysis,

**TABLE 1** Patient characteristics according to nodal status

	Overall series (n = 83)	Lymph nodes			P value <sup>a</sup>	P value <sup>b</sup>
		Positive (n = 11)	Negative (n = 27)	Not sampled (n = 45)		
Sex						
Male	37	6	11	20	0.491	0.646
Female	46	5	16	25		
Age, median (range), years	54 (22–76)	42 (24–73)	58 (22–74)	58 (34–76)	0.202	0.023
Histology						
Epithelial	72	9	24	39	0.615	1.00
Biphasic	10	2	2	6		
Sarcomatoid	1	–	1	–		
PCI						
Mean	20.4	21.5	15.3	23.5	0.083	0.001
Interval diagnosis-HIPEC, median (range)	4 (1–88)	4 (2–23)	4 (1–88)	4 (1–11)	0.562	0.512
Previous syst. CT						
Done	34	4	7	23	0.696	0.061
Not done	49	7	20	22		
Previous surgery						
Only biopsy	49	8	13	28	0.650	0.514
1 region dissected	22	2	9	11		
>1 region dissected	12	1	5	6		
ECOG						
0	61	8	21	32	1.00	0.605
1	16	3	4	9		
2	6	–	2	4		
CC-score						
0	28	5	13	10	0.611	0.071
1	38	4	12	22		
2–3	17	2	2	13		

<sup>a</sup> Pathologically negative versus positive nodes

<sup>b</sup> Pathologically negative versus positive/not sampled nodes

PCI peritoneal cancer index, HIPEC hyperthermic intraperitoneal chemotherapy, CT chemotherapy, ECOG Eastern Cooperative Oncology Group performance status, CC completeness of cytoreduction (CC-0 = no visible residual disease, CC-1 = residual disease ≤ 2.5 mm, CC-2 = residual disease > 2.5 mm and ≤ 25 mm, CC-3 = residual disease > 25 mm)

there was a statistical survival advantage ( $P = 0.005$ ) for the 27 patients with pathologically negative nodes as compared with the group of 56 with either positive or not assessed nodes (5-year survival 36.4%; median 26 months). On the contrary, no statistical survival difference was seen between patients with pathologically positive nodes and those with either negative or not assessed nodes ( $P = 0.079$ ).

At the time of the present analysis, three patients with metastatic nodes were alive with no evidence of disease, including the one with 21 positive nodes who was alive after 75 months, and two additional patients who were alive after 5 and 32 months, respectively. The remaining eight patients developed disease progression at 2–16 months (median 9 months), involving the liver parenchyma in one and the

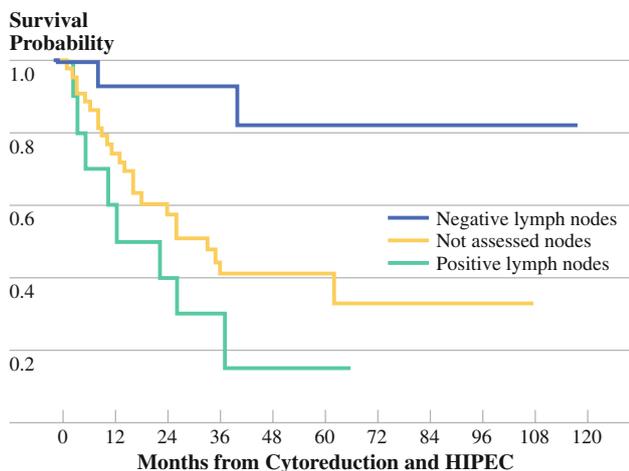
peritoneal surface in seven. No nodal recurrences occurred in these patients.

#### Survival by Distant Metastasis Status

Two patients with extra-abdominal extension of DMPM underwent cytoreduction and HIPEC since they had isolated metastatic disease amenable to complete surgical excision. In the first patient, DMPM presented with a laterocervical metastatic node. The second patient had tumor invasion of the abdominal wall at a previous laparoscopic port site. In addition, invasion of the tendinous portion of the diaphragm was detected in four patients during the cytoreductive surgical procedure. No statistical survival difference was associated with the presence of

**TABLE 2** Number of sampled and positive anatomic sites and lymph nodes

	Regions			Lymph nodes		
	Sampled	Positive		Sampled	Positive	
		<i>n</i>	<i>n</i>		%	<i>n</i>
Right common, internal, ext. iliac	20	6	33.3	92	22	23.9
Left common, internal, ext. iliac	11	2	18.2	51	4	7.8
Right inguinal	1	0	–	3	0	–
Left inguinal	1	1	100	14	6	42.9
Paracaval	2	1	50.0	9	5	55.6
Para-aortic	3	1	33.3	6	2	33.3
Epigastric	1	1	100	1	1	100
Gastrohepatic ligament	7	1	14.3	7	1	14.3
Omental	3	0	–	15	0	–
Splenic	1	0	–	2	0	–
Mesenteric	5	1	20.0	14	1	7.1
Ileocecal	2	1	50.0	5	1	20.0
Paracolic	7	2	28.6	57	2	3.5
Para-uterin	1	0	–	1	0	–
Total	65	17	26.2	277	45	16.2

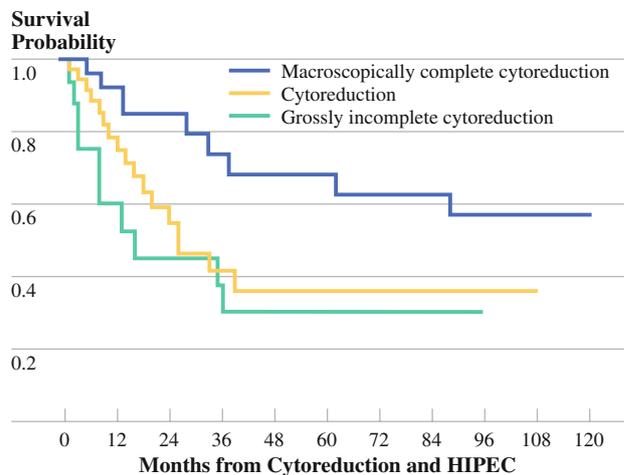


**FIG. 1** Overall survival according to nodal status. Survival was statistically better in patients with pathologically negative lymph nodes (blue line), as compared with those with not assessed (yellow line) nodes ( $P = 0.001$ ) and pathologically positive (green line) nodes ( $P = 0.009$ ); no significant survival difference was seen between pathologically positive nodes and nodes not submitted to pathological examination ( $P = 0.331$ )

extra-abdominal invasion. The patient with metastatic cervical node involvement is alive with no evidence of disease after 33 months.

*Prognostic Factors*

Overall survival according to completeness of cytoreduction is shown in Fig. 2. OS was statistically better in



**FIG. 2** Overall survival according to completeness of cytoreduction. Survival was statistically better in patients with macroscopically complete cytoreduction (blue line), as compared with those with (yellow line) nearly complete cytoreduction ( $P = 0.018$ ) and grossly incomplete (green line) cytoreduction ( $P = 0.006$ ); no significant survival difference was seen between nearly complete and grossly incomplete cytoreduction ( $P = 0.399$ )

patients undergoing complete cytoreduction, as compared with those undergoing nearly complete ( $P = 0.018$ ) or suboptimal cytoreduction (0.006). Median mitotic count was 5/50 HPF (mean 13.9; range 0–160).  $MC \leq 5/50$  HPF was associate with increased survival, as compared with higher mitotic rates ( $P = 0.001$ ).

Univariate and multivariate analyses of factors influencing survival are shown in Table 3. Three additional

**TABLE 3** Univariate and multivariate analysis of potential prognostic factors

	Overall series ( <i>n</i> = 83)				Patients with sampled nodes ( <i>n</i> = 38)	
	Univ.	Multivariate		Univ.	Multiv.	
	<i>P</i> value	HR	95%CI	<i>P</i> value	<i>P</i> value	
Sex	0.604				0.436	
Age (> 54 versus ≤ 54 years)	0.040	1.68	0.84–3.37	0.145	0.022	0.105
ECOG (1–2 versus 0)	0.142				0.016	0.543
Interval diagnosis-HIPEC (≤6 versus >6 months)	0.184				0.981	
Previous systemic CT	0.130				0.080	
Previous surgery (>1 versus ≤1 region dissected)	0.635				0.346	
Histology (biphasic/sarcomatoid versus epithelial)	0.024	2.93	1.24–6.95	0.015	0.613	
Mitotic count <sup>a</sup> (≤5 versus >5/50 HPF)	0.001	5.34	1.96–14.54	0.001	.278	
PCI (> 20 versus ≤ 20)	0.027	1.03	0.48–2.22	0.934	0.006	0.133
CC score (0 versus 1 versus 2–3)	0.018 <sup>b</sup>	2.06	1.19–3.56	0.001	0.504 <sup>b</sup>	0.679
	0.006 <sup>c</sup>				0.003 <sup>c</sup>	
Cytoreductive surgical proc. (≤4 versus >4)	0.216				0.180	
HIPEC drug schedule (cisplatin + mitomycin-C versus cisplatin + doxorubicin)	0.494				0.263	
Cisplatin total dosage	0.216				0.810	
Pathologically pos lymph nodes (versus neg./not sampled)	0.079	0.408	0.11–1.52	0.181	0.001	0.074
Pathologically neg. lymph nodes (versus pos./not sampled)	0.005	2.81	1.12–7.05	0.027	–	
Extra-abdominal metastases	0.838	1.26	0.19–8.52	0.811	0.383	
Serum CA125 (≤35 UI/ml versus >35 UI/ml) <sup>d</sup>	0.798				0.712	

HR hazard ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group performance status, HIPEC hyperthermic intraperitoneal chemotherapy, CT chemotherapy, HPH high-power field, PCI peritoneal cancer index, CC completeness of cytoreduction (CC-0 = no visible residual disease, CC-1 = residual disease ≤ 2.5 mm, CC-2 = residual disease > 2.5 mm and ≤ 25 mm, CC-3 = residual disease > 25 mm)

<sup>a</sup> Data available in 67 patients

<sup>b</sup> CC 0 versus 1

<sup>c</sup> CC 0 versus 2–3

<sup>d</sup> Data available in 68 patients

variables correlated with survival at univariate analysis: histological variant, age, and PCI. Epithelial histology, mitotic count ≤ 5/50 HPF, complete cytoreduction, and pathologically negative nodes were recognized by the Cox model as independent factors for increased survival.

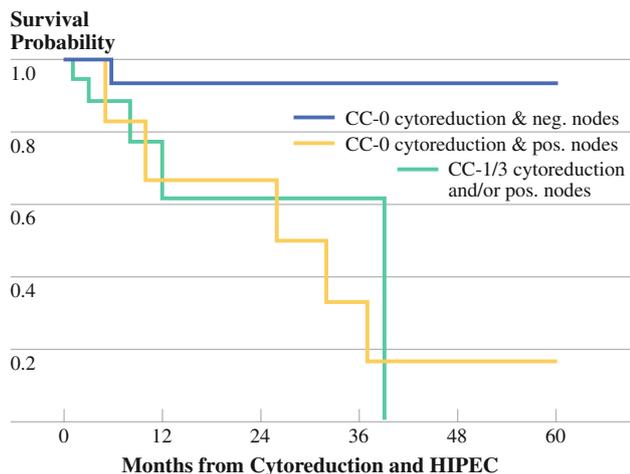
A further analysis was performed for the subset of patients with lymph nodes submitted to pathological examination. However, the Cox model did not identify any independent prognostic factors, apart for a trend toward significance for positive nodes. Figure 3 shows survival according to CC score combined with nodal status. Median survival was not reached for patients (*n* = 13) with CC-0 cytoreduction and pathologically negative nodes (median follow-up 63 months; range 6–138 months; 5-year OS 92.3%), as compared with 26 months for those (*n* = 6) with CC-0 cytoreduction and pathologically positive nodes (*P* = 0.002) and 39 months for those (*n* = 19) with CC-1/3 cytoreduction and/or positive nodes (*P* = 0.022); the survival difference between patients with CC-0 cytoreduction and positive nodes and those with CC-1/3

cytoreduction and/or positive nodes was not statistically significant (*P* = 0.691).

## DISCUSSION

For most tumors, prognosis depends on the extent to which the disease has invaded locally, involvement of regional lymph nodes, distant metastases, and histological or molecular features of tumor aggressiveness. No staging system is currently available to support the choice of treatment and prognostic assessment in peritoneal mesothelioma. The present study strongly suggests that nodal involvement, along with pathological characteristics such as histological subtype and mitotic count, are major prognostic determinants in patients undergoing combined treatment.

In recent years, an aggressive local-regional treatment approach has resulted in survival improvement for DMPM.<sup>4–11</sup> To date, the selection process for comprehensive management is based on patient factors and CT



**FIG. 3** Overall survival according to completeness of cytoreduction and nodal status combined. Survival was statistically better in patients ( $n = 16$ ) with CC-0 cytoreduction and pathologically negative nodes (blue line), as compared with those ( $n = 6$ ) with CC-0 cytoreduction and pathologically positive nodes (yellow line) ( $P = 0.002$ ) and those ( $n = 19$ ) with CC-1/3 cytoreduction and/or positive nodes (green line) ( $P = 0.022$ ); no significant survival difference was seen between patients with CC-0 cytoreduction and pathologically positive nodes and those with CC-1/3 cytoreduction and/or positive nodes ( $P = 0.691$ )

scan assessment, which has been demonstrated to reliably predict the likelihood to perform a complete cytoreduction.<sup>20</sup> Even after optimal cytoreduction, however, disease recurrences are not uncommon and represent a substantial cause of mortality. Additional prognostic factors are still poorly understood, since pathological and biological prognostic features have been addressed only in recent years, namely biphasic/sarcomatoid histology, mitotic count, telomerase activity, nuclear size, and p16 loss.<sup>8,9,11-13</sup> A more accurate prognostic assessment would be needed to design individualized multimodality treatment plans and to standardize supplementary therapeutic options for high-risk patients, such as second-look surgery, early postoperative intraperitoneal chemotherapy, and adjuvant systemic or targeted therapy.<sup>5,6,10,11,28</sup> In our institution, patients with nodal metastases are currently considered for postoperative systemic chemotherapy, and molecular-level investigations of receptor tyrosine kinase activation are

being performed to identify novel potential therapeutic approaches.<sup>29</sup>

In the present series, patients were categorized according to their nodal status. Overall survival was significantly better in patients with pathologically negative than in those with pathologically positive nodes. In patients with nodes not clinically suspicious and therefore not submitted to pathological examination, survival results were intermediate and not statistically different from those of patients with positive nodes. These data suggest that metastatic nodes could have remained undetected in patients with nodes not assessed by the pathologists. In fact, since routine node sampling became current practice in our institution, unexpected metastatic involvement was found in 20% of patients with nonsuspicious lymph nodes. Accordingly, a careful evaluation of node-containing sites is recommended when performing cytoreductive surgery for DMPM and all suspicious nodes should be submitted separately to pathological examination.

External, internal, and common iliac lymph nodes were the most common sites of metastatic involvement, suggesting that peritoneum has preferred drainage routes into the lymphatic system. The dynamics of intraperitoneal fluid in both normal patients and those affected by cancerous ascites has been studied.<sup>30,31</sup> Tumor-cell-containing fluids tend to accumulate in the pelvis, cul-de-sac of the ileocolic junction, and lesser sac. A relatively large cancer burden at these anatomic sites may result in regional lymph node metastasis, namely iliac, ileocolic, and gastrohepatic ligament nodes. Moreover, iliac lymph nodes have been demonstrated to be important sites of disease dissemination in primary peritoneal carcinoma.<sup>32</sup> Based on these data, we now routinely sample iliac and ileocolic lymph nodes in all patients with peritoneal mesothelioma undergoing comprehensive treatment.

The literature data on lymph node involvement in DMPM are summarized in Table 4. The only available focused series included 100 patients treated at the Washington Cancer Institute. Metastatic involvement was found in 7 of 21 patients with nodes submitted to pathologic examination, and node positivity correlated with reduced survival on multivariate analysis.<sup>15</sup> However, in two other studies by the same institution, an exhaustive histopathological series and a

**TABLE 4** Literature information on lymph node involvement in peritoneal mesothelioma

NA not available, NS not significant

<sup>a</sup> Pathologically negative versus pathologically positive/not sampled

Author	Pts (n.)	Sampled nodes (%)	Positive nodes (%)	Univ. <i>P</i> value	Multiv. <i>P</i> value
Borczuk et al. <sup>11</sup>	54	NA	13	0.041	NS
Yan et al. <sup>15</sup>	100	21	7	<0.001	<0.001
Cerruto et al. <sup>13</sup>	62	NA	11	<0.001	NS
Yan et al. <sup>9</sup>	62	NA	11	0.069	–
Present series	83	46	14	0.005 <sup>a</sup>	0.027 <sup>a</sup>

prognostic analysis of clinical and radiological features, nodal metastases lacked independent prognostic significance.<sup>9,13</sup> Finally, in a series of 54 patients receiving either no therapy, systemic chemotherapy, or trimodal therapy (cytoreduction, HIPEC, and abdominal radiation) at the Columbia University Medical Center, nodal involvement occurred in 13% of cases and correlated with survival on univariate but not multivariate analysis.<sup>11</sup>

Our conclusions are consistent with the Washington Cancer Institute in that node involvement correlates with prognosis.<sup>15</sup> Our study clearly demonstrated that pathologically negative nodes independently correlate with better prognosis, as compared with positive/not sampled nodes. However, unlike the Washington Cancer Institute, we were unable to demonstrate any statistical survival difference when we compared patients with pathologically positive lymph nodes with the subset of those with either pathologically or clinically negative nodes, assuming not suspicious, not sampled nodes as uninvolved. These findings are likely related to the higher percentage of patients with sampled and positive nodes in our series suggest that a policy of accurate node assessment can identify cases with early lymphatic spread and better prognosis. Another explanation for the discrepancy between our findings and those of Yan et al. may be due to the fact that all the patients with nodal metastases at the Washington Cancer Institute died within 2 years, while three node-positive patients of the present series are still alive, including two long-term survivors, one with 21 metastatic nodes.<sup>15</sup> This dissimilarity in survival may be related to the increasingly aggressive local-regional chemotherapy regimens used over the years at the Washington Center, as compared with the use of a standardized protocol in all patients at our institution, with minimal treatment-related bias.<sup>5,15</sup>

Cervical lymph node metastasis as the initial manifestation of malignant mesothelioma occurred in one patient of the present series, who is presently alive after 33 months. This presentation was firstly described in four patients by Rosai and Sussmann in 1990 and, to the best of our knowledge, no other case has been reported in the literature.<sup>14</sup>

Presumably due to the limited penetration of intraperitoneal chemotherapy into residual peritoneal disease, increased survival independently correlated with complete cytoreduction and with pathological features, such as epithelial histology and low mitotic count. Although most DMPM have relatively low mitotic rate, our and other groups have reported that higher MC is associated with poor outcome.<sup>8,11,18</sup> However, other authors did not reach the same conclusion.<sup>33</sup> Analogously, the adverse impact of biphasic/sarcomatoid histology has been reported previously.<sup>11,13</sup> In a further analysis, we tried to combine CC score and nodal status to determine whether additional

prognostic information could be provided. Survival was statistically better in patients with CC-0 cytoreduction and pathologically negative nodes, as compared with those with CC-0 cytoreduction and pathologically positive nodes and those with CC-1/3 cytoreduction and/or positive nodes. Also, no significant survival difference was seen between the latter groups, suggesting that metastatic node involvement would confer the same adverse prognosis of suboptimal cytoreduction even if complete tumor removal is accomplished. A larger number of patients would be needed to better define reliable prognostic categories.

The connections between lymphatic and systemic circulation make it more likely that distant metastases will occur in patients with lymph node involvement. Nevertheless, the analysis of the pattern of failure among the 11 patients with lymph node involvement showed that peritoneal progressive disease occurred in seven patients, liver metastasis in one, and nodal metastases in none. This suggests that nodal metastases may be related to local rather than systemic tumor aggressiveness and further supports the rational base of aggressive local-regional management of this disease.

In conclusion, pathologically negative lymph nodes identify a subset of patients with better prognosis following cytoreduction and HIPEC. Clinical node assessment may be insufficiently accurate, and careful sampling of the most commonly involved node sites is recommended. Nodal status, along with biological and pathological markers of tumor aggressiveness, may be considered for the development of a new staging system for DMPM.

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## REFERENCES

1. Markman M, Kelsen D. Efficacy of cisplatin-based intraperitoneal chemotherapy as treatment of malignant peritoneal mesothelioma. *J Cancer Res Clin Oncol.* 1992;118:547–50.
2. Neumann V, Muller KM, Fischer M. Peritoneal mesothelioma: incidence and aetiology. *Pathologe.* 1999;20:169–76.
3. Eltabbakh GH, Piver MS, Hempling RE, Recio FO, Intengen ME. Clinical picture, response to therapy, and survival of women with diffuse malignant peritoneal mesothelioma. *J Surg Oncol.* 1999;70:6–12.
4. Loggie BW, Fleming RA, McQuellon RP, Russel GB, Levine EA. Prospective trial for the treatment of malignant peritoneal mesothelioma. *Am Surg.* 2001;67:999–1003.
5. Sugarbaker PH, Welch LS, Mohamed F, Glehen O. A review of peritoneal mesothelioma at the Washington Cancer Institute. *Surg Oncol Clin North Am.* 2003;12:605–21.
6. Feldman AL, Libutti SK, Pingpank JF, et al. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. *J Clin Oncol.* 2003;21:4560–7.

7. Brigand C, Monneuse O, Mohamed F, Sayag-Beaujard AC, Isaac S, Gilly FN, et al. Malignant peritoneal mesothelioma treated by cytoreductive surgery and intraperitoneal chemohyperthermia: results of a prospective study. *Ann Surg Oncol.* 2006;13:405–12.
8. Deraco M, Nonaka D, Baratti D, et al. Prognostic analysis of clinicopathologic factors in 49 patients with diffuse malignant peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion. *Ann Surg Oncol.* 2006;13:229–37.
9. Yan TD, Brun EA, Cerruto CA, Haveric N, Chang D, Sugarbaker PH. Prognostic indicators for patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma. *Ann Surg Oncol.* 2007;14:41–9.
10. Elias D, Bedard V, Bouzid T, Duvillard P, Kohneh-Sharhi N, Raynard B, et al. Malignant peritoneal mesothelioma: treatment with maximal cytoreductive surgery plus intraperitoneal chemotherapy. *Gastroenterol Clin Biol.* 2007;31:784–8.
11. Borczuk AC, Taub RN, Hesdorffer M, et al. P16 loss and mitotic activity predict poor survival in patients with peritoneal malignant mesothelioma. *Clin Cancer Res.* 2005;11:3303–8.
12. Villa R, Daidone MG, Motta R, et al. Multiple mechanisms of telomere maintenance exist and differentially affect clinical outcome in diffuse malignant peritoneal mesothelioma. *Clin Cancer Res.* 2008;14:4134–40.
13. Cerruto CA, Brun EA, Chang D, Sugarbaker PH. Prognostic significance of histomorphologic parameters in diffuse malignant peritoneal mesothelioma. *Arch Pathol Lab Med.* 2006;130:1654–61.
14. Sussman J, Rosai J. Lymph node metastasis as the initial manifestation of malignant mesothelioma. Report of six cases. *Am J Surg Pathol.* 1990;14:819–28.
15. Yan TD, Yoo D, Sugarbaker PH. Significance of lymph node metastasis in patients with diffuse malignant peritoneal mesothelioma. *Eur J Surg Oncol.* 2006;32:948–53.
16. González-Moreno S, Brun E, Sugarbaker PH. Lymph node metastasis in epithelial malignancies of the appendix with peritoneal dissemination does not reduce survival in patients treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Ann Surg Oncol.* 2005;12:72–80.
17. Angioli R, Plotti F, Palaia I, et al. Update on lymphadenectomy in early and advanced ovarian cancer. *Curr Opin Obstet Gynecol.* 2008;20:34–9.
18. Nonaka D, Kusamura S, Baratti D, et al. Diffuse malignant mesothelioma of the peritoneum. *Cancer.* 2005;104:2181–8.
19. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649–55.
20. Yan TD, Haveric N, Carmignani CP, Chang D, Sugarbaker PH. Abdominal computed tomography scans in the selection of patients with malignant peritoneal mesothelioma for comprehensive treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Cancer.* 2005;103:839–49.
21. Rossi CR, Foletto M, Mocellin S, et al. Hyperthermic intraoperative intraperitoneal chemotherapy with cisplatin and doxorubicin in patients who undergo cytoreductive surgery for peritoneal carcinomatosis and sarcomatosis: phase I study. *Cancer.* 2002;94:492–99.
22. Esquivel JE, Sugarbaker PH. Elective surgery in recurrent colon cancer with peritoneal seeding: when to and when not to. *Cancer Ther.* 1998;1:321–5.
23. Jaquet P, Sugarbaker PH. Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. *J Exp Clin Cancer Res.* 1996;15:49–58.
24. Battifora H, McCaughey WTE. Tumors of the serosal membranes. Atlas of tumor pathology, 3rd series, fascicle 15. Washington, DC: Armed Forces Institute of Pathology; 1994.
25. Therasse P, Arbusk SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205–16.
26. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Soc.* 1958;53:457–81.
27. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc B.* 1972;34:187–220.
28. Foster JM, Gatalica Z, Lilleberg S, Haynatzki G, Loggie BW. Novel and existing mutations in the tyrosine kinase domain of the epidermal growth factor receptor are predictors of optimal resectability in malignant peritoneal mesothelioma. *Ann Surg Oncol.* 2009;16:152–8.
29. Perrone F, Jocolle G, Brich S, Cabras AD, Deraco M, Baratti D, et al. analysis of EGFR, PDGFRA, PDGFRB and related pathways in malignant peritoneal mesothelioma. The 9th International Conference of the International Mesothelioma Interest Group (Abstract 217).
30. Carmignani CP, Sugarbaker CA, Bromley CM, Sugarbaker PH. Intraperitoneal cancer dissemination: mechanisms of the pattern of spread. *Cancer Metastasis Rev.* 2003;22:465–72.
31. Meyer MA. Distribution of intraabdominal malignant seeding: dependency on dynamics of flow of ascitic fluid. *Am J Roentgenol Radium Ther Nucl Med.* 1973;119:198–206.
32. Eltabbakh GH, Mount SL. Lymphatic spread among women with primary peritoneal carcinoma. *J Surg Oncol.* 2002;81:126–31.
33. Kerrigan SA, Turnnir RT, Clement PB, Young RH, Churg A. Diffuse malignant epithelial mesotheliomas of the peritoneum in women: a clinicopathologic study of 25 patients. *Cancer.* 2002;94:378–85.