Original Article

A Novel Tumor-Node-Metastasis (TNM) Staging System of Diffuse Malignant Peritoneal Mesothelioma Using Outcome Analysis of A Multi-institutional Database

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BACKGROUND: Currently, no tumor-node-metastasis (TNM) staging system exists for patients with diffuse malignant peritoneal mesothelioma (DMPM). The primary objective was to formulate a clinicopathological staging system through the identification of significant prognostic parameters. **METHODS:** Eight international institutions with prospectively collected data on patients who underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy contributed to the registry. Two hundred ninety-four patients had complete clinicopathological data and formed the basis of this staging project. **RESULTS:** Peritoneal cancer index (PCI) was categorized into T_1 (PCI 1-10), T_2 (PCI 11-20), T_3 (PCI 21-30), and T_4 (PCI 30-39). Twenty-two patients had positive lymph nodes (N_1) and 12 patients had extra-abdominal metastases (M_1). The survival for patients with T_1 (PCI 1-10) N_0 M_0 was significantly superior to the other patients. This group of patients is therefore designated as Stage I. The survival of patients with T_2 (PCI 11-20) and T_3 (PCI 21-30), in absence of N_1 or M_1 disease, was similar. This group of patients was categorized as Stage II. The survival of patients with T_4 (PCI 30-39), N_1, and/or M_1 was similarly poor. This group of patients was therefore categorized as Stage III. Three prognostic factors were independently associated with survival in the multivariate analysis: histological subtype, completeness of cytoreduction, and the proposed TNM staging. The 5-year survival associated with Stage I, II, and III disease was 87%, 53%, and 29%, respectively. **CONCLUSIONS:** The proposed TNM staging system resulted in significant stratification of survival by stage when applied to the current multi-institutional registry data. ***Cancer*** **2010;000:000–000.** © *2010 American Cancer Society.*

KEYWORDS: Peritoneal mesothelioma, cytoreductive surgery, peritonectomy, hyperthermic intraperitoneal chemotherapy.

Precise, globally accepted staging systems are key to assessing treatment outcomes, comparing results across institutions, designing and analyzing clinical trials, and selecting therapy for individual patients. Currently, no tumor-node-metastasis (TNM) staging system exists for patients with diffuse malignant peritoneal mesothelioma (DMPM), because the disease is rare and no effective therapies were available. In this disease with a unique natural history, the new system requires a logical application of TNM to the primary disease state that is usable by the clinician on a routine basis.

Recently, cytoreductive surgery (CRS), combined with hyperthermic intraperitoneal chemotherapy (HIPEC), has emerged as a treatment option that offers a prolonged survival in selected patients, achieving a median survival of up to 60 months and a 5-year survival of 50%.[1-5] With this multimodality treatment approach, complete macroscopic cytoreduction is performed. Importantly, this allows adequate tumor specimens to be analyzed.

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In an attempt to formulate a clinical staging system with sufficient statistical power, a multi-institutional data registry on peritoneal mesothelioma was established during the 6th International Workshop on Peritoneal Surface Malignancy in Lyon in late 2008. Eight international institutions with prospectively collected data on patients who underwent treatment consisting of CRS and HIPEC contributed to the registry. The primary objective was to formulate a clinicopathological staging system through identification of statistically significant prognostic parameters.

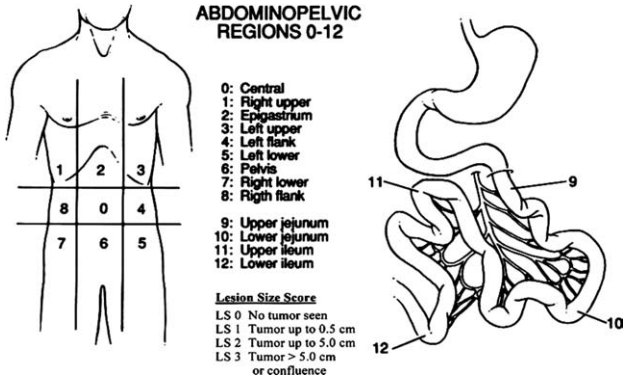


Figure 1. Peritoneal cancer index (PCI).

MATERIALS AND METHODS

Patient Population

Ethics approval was obtained from the participating institutions through their IRB—or the chairperson of the ethics committee who waived the need for patient consent for the study, as individual patients were not identified. Between October 1989 and February 2009, the present multi-institutional registry collected data on 405 patients with DMPM, who were considered preoperatively to be candidates for CRS and HIPEC. Of these 405 patients, peritoneal cancer index (PCI) was unknown in 110 patients and follow-up data were unavailable in 4 patients. A total of 294 patients with complete clinicopathologic and follow-up data were included in this staging project.

All of the included patients had peritoneal mesothelioma confirmed by histopathologic examination and a treatment strategy that used CRS followed by HIPEC. Peritonectomy and visceral resections were performed at the sites of disease involvement, with intent to remove all tumor deposits together with involved peritoneum. CRS was performed according to protocol Sugarbaker described previously.[6] In short, peritonectomy procedures include total anterior parietal peritonectomy, omentectomy ± splenectomy, right and left subphrenic peritonectomy, pelvic peritonectomy ± rectosigmoid colon resection, lesser omentectomy ± cholecystectomy, and ± peritonectomy of the omental bursa.[6] All HIPEC procedures were performed intraoperatively after CRS. The most common HIPEC regimen was cisplatin combined with doxorubicin, and paclitaxel for early perioperative intraperitoneal chemotherapy. It is acknowledged that there were variations in intraperitoneal chemotherapy exposure techniques (open or closed), duration (30 to 120 minutes), and intraperitoneal temperatures (40°C to 43°C) among the institutions. However, all studies shared the 2 most important concepts in treatment rationale: maximal cytoreduction to remove macroscopic disease and intraperitoneal chemotherapy delivered immediately after CRS to eradicate residual tumor cells. The multiple specimens of gross disease available in all patients provided the clinical material for a thorough assessment of lymph node status and tumor invasion.

Standardized Data Form

A blinded standard data form was created to retrieve relevant clinical/pathologic data, including age, sex, date of surgery, extent of prior surgical intervention and performance status, histopathologic subtype, peritoneal cancer index (PCI), presence of lymph node metastasis, presence of extra-abdominal metastasis, and completeness of cytoreduction. These variables were included in the subsequent data analysis for overall survival. The volume and extent of the tumor deposits were prospectively recorded using the PCI.[7] This assessment combines lesion size (0 to 3) with tumor distribution (abdominopelvic region 0 to13) to quantify the extent of disease as a numerical score (PCI-0 to 39) (Fig. 1).[7] Sites and volumes of the residual disease after CRS were also prospectively recorded using the completeness of cytoreduction (CC) Score.[7] A CC-0 indicated no visible evidence of disease, CC-1 indicated residual tumors $\leq$2.5 mm in diameter, CC-2 indicated residual tumors between 2.5 mm and 2.5 cm in diameter, and CC-3 indicated residual tumors >2.5 cm in diameter or a confluence of tumor nodules present at any site. Standardized clinical data on consecutive patients from each of the 8 institutions were entered into a central database. Follow-up data from most recent reviews were included, consisting of clinical examination and assessment of abdominopelvic CT scans. Each institution confirmed that the pooled data represented consecutive

operative procedures performed in the study period by participating surgeons.

Statistical Analysis

The data were reported on intention-to-treat basis; ie, all patients were selected for the combined procedure, irrespective of completeness of cytoreduction or whether HIPEC was given or not. Perioperative mortality was included in the overall survival analysis. Overall survival was used as the primary endpoint, which was determined from the time of surgery. Survival analysis was performed by using the Kaplan-Meier method and compared using the log-rank test. For multivariate analysis, a Cox proportional hazards model (with forward stepwise selection of covariates and entering/removing limits of $P < .10$ and $P > .05$) was used. All statistical analyses were performed using the Statistical Package for Social Sciences for Windows (Version 17.5; SPSS GmbH, Munich Germany). A significant difference was defined as $P < .05$.

RESULTS

Analysis of Standardized Data Form

The mean age at the time of CRS was 50 (S.D. = 14) years. There were 159 (54%) male patients. Two hundred fifty-nine patients (88%) had epithelial and 27 patients (9%) had biphasic or sarcomatoid tumors. Twenty-two patients (7%) had lymph node metastases. Twelve patients (4%) had extra-abdominal metastatic disease in the form of disease penetrating the diaphragm or old abdominal wall scar, which was resected at the time of CRS. The mean PCI was 20 (S.D. = 10). At the end of surgery, 74 patients (25%) had CC-0 cytoreduction, 64 patients (22%) had CC-1 cytoreduction, 39 patients had CC-2 cytoreduction (13%), and 35 patients (12%) had CC-3 cytoreduction.

Survival Outcome

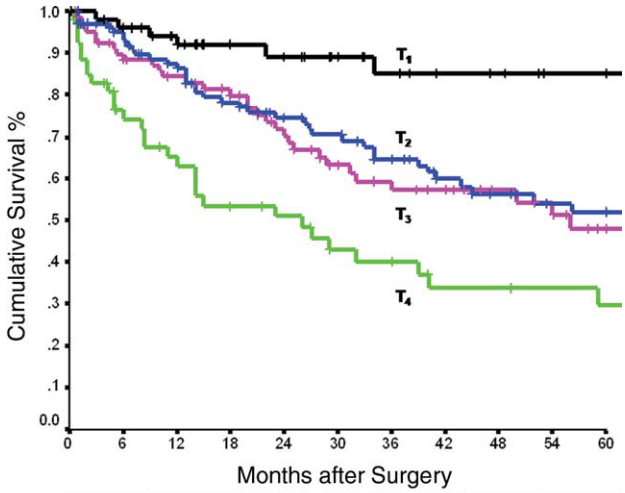
One hundred nine patients (37%) were deceased at the last-time follow-up. The median follow-up period was 24 months (range 1 to 235 months). The overall median survival was 67 months (range 1 to 235 months), with 1-, 3-, and 5-year survival of 83%, 62% and 52%, respectively. Univariate analysis identified 7 significant prognostic variables associated with improved survival: age ≤ 50 ($P = .011$), female ($P < .001$), epithelial subtype ($P = .006$), PCI 1-10 ($P < .001$), absence of lymph node metastasis ($P < .001$), absence of extra-abdominal metastasis ($P = .004$), and CC-0/1 ($P < .001$) (Table 1).

Table 1. Univariate Analysis of Clinicopathologic Factors Affecting Survival

Variable	No. of Patients	Median Survival, Mo	P
Total	294	67	—
Age at the time of surgery	—	—	.011
≤50 years	143	NR	—
>50 years	151	45	—
Gender	—	—	<.001
Male	159	41	—
Female	135	119	—
Extent of prior surgery	—	—	.997
Limited dissection or biopsy	118	54	—
Previous surgical debulking	56	67	—
Unknown	120	—	—
Performance status	—	—	.670
≤2	171	67	—
>2	33	76	—
Unknown	90	—	—
Histologic subtype	—	—	<.001
Epithelial	259	79	—
Biphasic/sarcomatoid	27	10	—
Unknown	8	—	—
Peritoneal cancer index	—	—	<.001
1-10	54	NR	—
11-20	106	67	—
21-30	81	56	—
31-39	53	26	
Lymph node metastasis	—	—	<.001
Present	22	20	—
Absent	272	76	—
Extra-abdominal metastasis	—	—	.004
Present	12	20	—
Absent	282	76	—
Completeness of cytoreduction	—	—	<.001
CC-0/1	139	NR	—
CC-2/3	73	26	
Unknown	82	—	—

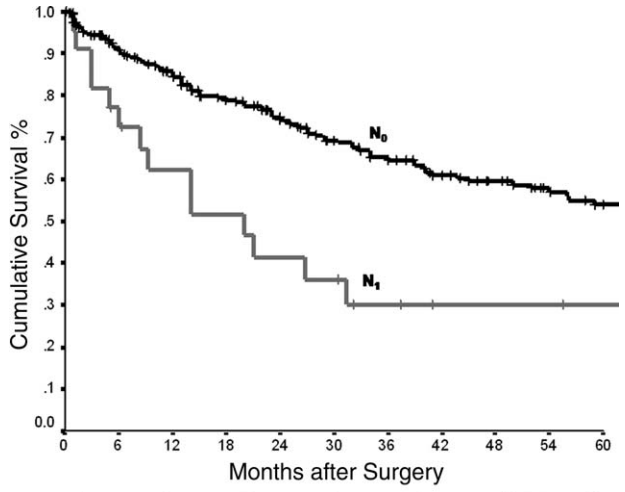
Selection of Data to be Utilized as a TNM Staging System

Among these 7 significant prognostic factors, age, gender, and histopathologic subtype are intrinsic (ie, they are not influenced by disease progression), and CC score can only be determined postoperatively. Therefore, these parameters were not suitable for preoperative staging. The remaining 3 significant prognostic parameters (PCI, lymph node status, and extra-abdominal metastasis) were selected for formulating the clinicopathological staging system.



T Stage	PCI	N	Median	1-year	3-year	5-year
T1	1-10	54	Not reached	92	85	85
T2	11-20	106	67	86	65	52
T3	21-30	81	56	84	57	48
T4	31-39	53	26	63	40	30

Figure 2. Overall survival stratified by peritoneal cancer index into novel T stages (n = 294).



N Stage	N	Median	1-year	3-year	5-year
N0	272	76	84	64	54
N1	22	20	62	30	30

Figure 3. Overall survival stratified by lymph node status (n = 294).

T factor—peritoneal cancer index

In the present analysis, PCI was categorized into 4 subgroups: T_1 (PCI 1-10), T_2 (PCI 11-20), T_3 (PCI 21-30), and T_4 (PCI 30-39), and associated with significant difference in survival (Fig. 2). The number of patients was similar in low PCI (T_1) and high PCI (T_4) subgroups. Fifty-four patients were categorized into T_1 subgroup, with 1-, 3- and 5-year survival rates of 92%, 85%, and 85%, respectively. One hundred six patients were categorized into T_2 subgroup and had a median survival of 67 months, with 1-, 3-, and 5-year survival rates of 86%, 65%, and 52%, respectively. Eighty-one patients were categorized into T_3 subgroup and had a median survival of 56 months, with 1-, 3-, and 5-year survival rates of 84%, 57%, and 48%, respectively. Fifty-three patients were categorized into T_4 subgroup and had a median survival of 26 months, with 1-, 3-, and 5-year survival rates of 63%, 40%, and 30%, respectively.

N factor—lymph node status

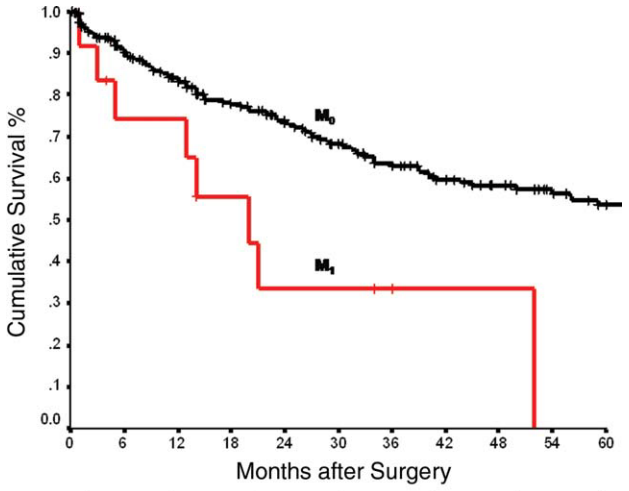
Twenty-two patients were found to have positive lymph nodes (N_1) during surgical exploration. Their median survival was 20 months, with 1- and 3-year survival rates of 62% and 30%, respectively. The median survival for the patients without positive lymph nodes (N_0) was 76 months and 1-, 3-, and 5-year survival rates were 84%, 64%, and 54%, respectively (Fig. 3). The most common sites for positive lymph nodes were external, internal, and common iliac lymph nodes. Ten patients had positive retroperitoneal lymph nodes located along the external, internal, and common iliac vessels. Among these 10 patients, 1 also had positive gastrohepatic ligament nodes; 1 had epigastric, left inguinal, paracaval, and para-aortic nodes; and 1 had positive ileocolic, right deep inferior epigastric, and right inguinal nodes. Four patients had positive ileocolic lymph nodes only. Two patients had positive mesenteric lymph nodes only. Two patients had positive lymph nodes located in the gastrohepatic ligament only.

M factor—extra-abdominal disease

Twelve patients had extra-abdominal metastatic disease (M_1) in the form of tumor penetrating the diaphragm (or old abdominal wall scar), which was resected at the time of CRS. Despite resection, the prognosis for these patients was markedly poorer than the patients without extra-abdominal metastasis (M_0) (Fig. 4). The median survival for M_0 disease was 76 months, with 1-, 3-, and 5-year survival of 83%, 63%, and 54%, respectively. In contrast, the median survival of M_1 disease was 20 months, with 1-, 3-, and 5-year survival of 74%, 33%, and 0%, respectively.

Superimposed survival curves consisting of PCI, lymph node status, and extra-abdominal metastasis are demonstrated in Figure 5 ($P < .001$). The figure demonstrated that 1) the survival for patients with T_1 (PCI 1-10) N_0 M_0 was significantly superior and therefore designated

as Stage I DMPM; 2) the survival outcomes of patients with T_2 (PCI 11-20) and T_3 (PCI 21-30) in absence of N_1 or M_1, were similar, and therefore they should be categorized as Stage II DMPM; and 3) the survival outcomes of patients with T_4 (PCI 30-39), N_1, and/or M_1 were similarly poor, and therefore should be categorized as Stage III disease. The proposed TNM staging system (Table 2) resulted in significant stratification of survival by stage when applied to the current multi-institutional registry data (Fig. 6). The 5-year survival for patients with Stage I, II, and III disease was 87%, 53%, and 29%, respectively.



M Stage	N	Median	1-year	3-year	5-year
M0	282	76	83	63	54
M1	12	20	74	33	0

Figure 4. Overall survival stratified by extra-abdominal metastasis (n = 294).

Multivariate Analysis

The significant prognostic variables identified in univariate analysis, including age, gender, subtype, the proposed clinical staging system, and CC score, were entered into a Cox proportional hazards model. Three prognostic factors were independently associated with survival in the multivariate analysis: biphasic/sarcomatoid subtypes versus epithelial subtype ($P < .001$; hazard ratio: 5.507; 95% confidence interval [CI], 2.877-10.540); CC-2/3 versus CC-0/1 ($P = .005$; hazard ratio: 1.983; 95% CI, 1.225-3.209); and the proposed TNM staging system ($P < .001$; stage II vs stage I hazard ratio: 3.313; 95% CI, 1.153-9.435; stage III vs stage I hazard ratio: 5.952; 95% CI, 2.054-17.248).

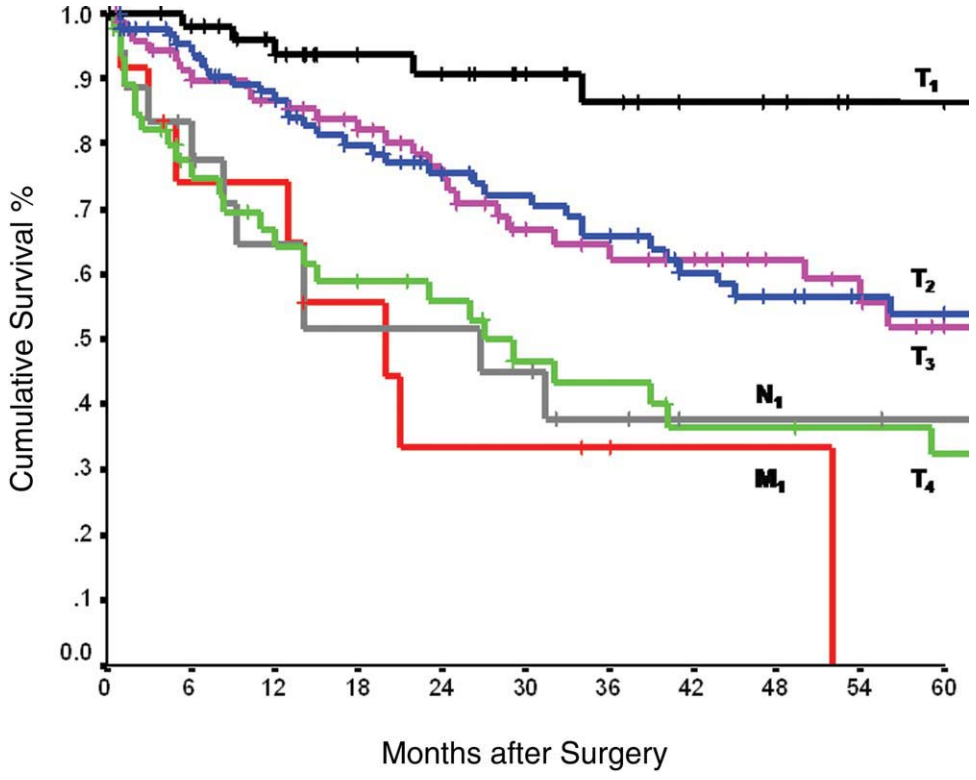


Figure 5. Superimposed survival curves stratified by T, N, and M factors (n = 294).

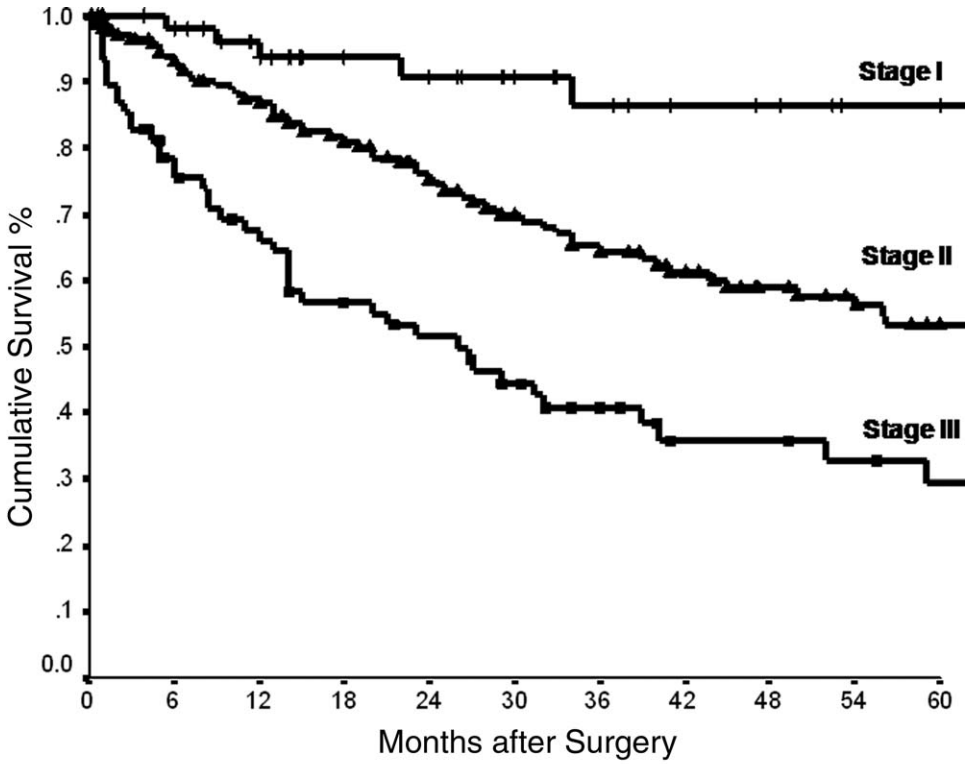
DISCUSSION

The aim of establishing a clinical staging system for DMPM is to allow clinicians to identify the most appropriate surgical candidates, stratify treatment regimens, and more accurately predict prognosis. In the past DMPM was regarded as a terminal disease, and no effective therapies existed.[8] Because of the localized nature of the disease, a renewed interest in selecting appropriate surgical candidates for the combined treatment approach involving CRS and HIPEC has emerged in recent years. This is encouraged by promising treatment outcomes published by several specialist centers worldwide.[1-5] As DMPM evolves into a surgically treatable disease, a globally accepted staging system is needed to allow meaningful comparisons and evaluations.

Because of the unusual natural history of DMPM, lack of a TNM system in DMPM is not surprising. The T stage is diffuse disease widely dispersed on peritoneal surfaces. Also, the disease is rare, and most centers do not have a sufficient number of patients to statistically evaluate results of treatment. Before CRS and HIPEC, treatments used in these patients varied greatly. Most studies in the current literature have a relatively small sample size, and the clinical implications of these reports, in terms of their value for patient management, are limited. The present registry represents a collaborative effort demonstrating

Table 2. Proposed TNM Stage Grouping for Diffuse Malignant Peritoneal Mesothelioma

Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2-3	N0	M0
III	T4	N0-1	M0-1
	T1-4	N1	M0-1
	T1-4	N0-1	M1



Stage	N	Median	1-year	3-year	5-year
I	52	Not reached	94	87	87
II	166	67	87	64	53
III	76	26	66	41	29

Figure 6. Overall survival stratified by proposed TNM staging system (n = 294).

clinical outcomes of peritoneal mesothelioma patients treated by the combined treatment strategy. This comprehensive analysis enabled the unambiguous retrospective audit of key clinicopathological features in the multi-institutional registry required for establishing an outcome-based staging system. From our database we demonstrated that the prognosis of patients with DMPM, as with a majority of other solid tumors, is largely determined by tumor pathology (histopathologic subtype), surgical intervention (completeness of cytoreduction), and TNM staging. The proposed TNM staging system involves distinct clinical and pathological parameters, where the T factor is examined *intraoperatively* at the time of exploratory laparotomy, N factor is examined during *histopathology* of the surgical specimens, and M factor is examined *preoperatively* using various imaging techniques.

Tumor pathology

The pathological classification of DMPM consists of epithelial, sarcomatoid, and biphasic types.[9] Survival of the nonepithelial subtype is extremely poor.[4] However, the clinical significance of this finding is restricted, because of the small percentage of patients with the nonepithelial subtype in DMPM. Based on current clinical data, the combined procedure is not recommended to patients with nonepithelial subtype. The first attempt to formulate a pathologic grading system for DMPM was by Goldblum and Hart in 1995.[10] They described a nuclear grading system, which categorized nuclear size into 4 grades. Kerrigan and colleagues first tested this nuclear grading system in 25 female patients with DMPM who underwent a variety of surgical, chemotherapy, or radiotherapy treatments and found that the nuclear grading was not strongly associated with long-term survival.[11] Yan and colleagues recently demonstrated nuclear size was the only independent prognostic factor for overall survival in 62 patients.[5] The 3-year survival rates with nuclear size of 10-20 μm, 21-30 μm, 31-40 μm and >40 μm were 100%, 87%, 27%, and 0%, respectively. However, the relationship of increasing nuclear size to a tumor's aggressive biological behavior has not been determined, and the reproducibility of the pathologic grading system derived from nuclear size needs to be validated in larger prospective cohorts.

Completeness of cytoreduction

Nearly all peritonectomy centers agree that adequate cytoreduction is one of the most significant prognostic factors for long-term survival.[1-5] However, there are problems with using CC score for staging DMPM, as this prognostic information is unavailable preoperatively in the patient selection process. In an attempt to predict the likelihood of achieving complete cytoreduction, Yan et al published a radiologic staging system for DMPM showing that interpretive CT findings of the small bowel and mesentery are useful in determining operability of a patient with DMPM.[12] Small volume disease in abdominopelvic region II (epigastric region) or Class I/II small bowel regions indicating no distortion of gross anatomy identifies patients likely to receive complete cytoreduction. Conversely, in Class III disease, whereby the small bowel and mesentery on CT appear so thickened and grossly distorted, complete cytoreduction is never achievable. Knowledgeable use of preoperative CT allows the oncologist to avoid extensive treatments in patients unlikely to benefit.

Proposed TNM staging system

For most solid tumors, the disease process has been effectively modeled in terms of assessment of the primary lesion (T factor), lymphatic spread (N factor), and distant metastasis (M factor), expressed in a TNM staging framework.[13] With better understanding of the natural history of DMPM, it is realized that the disease is initially confined to the peritoneal cavity and rarely metastasizes to lymph node and distant sites, unless in the advanced stage. As DMPM becomes a surgical disease, developing a TNM staging is plausible.

The use of PCI is the innovation that causes our present proposal to function for DMPM as a surrogate for T stage. In this disease, no single primary tumor is the focus for subsequent cancer spread and metastases. Rather, at diagnosis thousands of mesothelioma nodules are present, widely distributed on peritoneal surfaces. To quantify the diffuse peritoneal cancer dissemination, we suggest the PCI be used to measure the extent of the primary disease. The PCI has been validated as an accurate metric of peritoneal surface dissemination.[14-16] The T factor (as examined in this study) is performed intraoperatively through PCI scoring. Whether a preoperative T factor may be classified using radiological scoring of the PCI remains uncertain, owing to the failures of modern imaging techniques on capturing peritoneal disease.[17]

Another important finding about DMPM recently uncovered regards the necessary assessment of lymph node status as part of the CRS. Several reports have shown that nodal dissemination is one of the most significant

indicators for survival.[18,19] Lymph node metastases are uncommon in patients with DMPM, but when they occur they are associated with a poor prognosis. Data from the Washington Cancer Institute showed that 7 patients had positive lymph nodes.[18] Their median survival was 6 months, with 1- and 2-year survival of 43% and 0%, respectively. Ninety-three patients had absence of lymph node involvement and their median survival was 59 months, with 5- and 7-year survival of 50% and 43%, respectively.[18] Baratti and coworkers demonstrated a 5-year survival of 82.5% for patients with pathologically negative lymph nodes, compared with 16.7% for those with positive lymph nodes.[19] Inclusion of a N stage in a TNM system for DMPM may lead to improved intraoperative assessment of the prognosis. The crucial importance of lymph node metastasis should encourage surgeons to vigorously search for abnormal appearing nodes when performing CRS. Any enlarged or firm lymph nodes should be submitted for pathological evaluation separately from the rest of the specimens. It should become current surgical practice to sample all suspicious lymph nodes, identify their location, and submit them separately in patients with DMPM to better determine prognosis and provide more knowledge in the management of these patients.

In this series, 12 patients had extra-abdominal metastatic disease in the form of disease penetrating the diaphragm, and 2 patients also had disease invading through the old abdominal wall scar. Although the extra-abdominal disease was resected at the time of surgery, the prognosis for these 12 patients was markedly poorer than the patients without extra-abdominal metastasis. This may represent the biologically invasive nature of the tumor, and the prognosis of this subgroup of patients should be guarded. It must be emphasized that the total number of patients with nodal disease and distant metastases was small, as these patients are often not candidates for the combined treatment. Hence, adequate characterization of subgroups within this patient cohort with advanced disease is not possible through this registry. Patients with advanced disease (ie, stage III) in this study nevertheless still showed encouraging survival results with median survival of 26 months. It is likely that the patients with more advanced disease (those excluded from the combined treatment) would be classified as stage IV disease.

The proposed clinicopathologic staging system is based exclusively on patients treated with CRS and HIPEC. It emphasizes the prognostic importance of tumor volume and distribution within the peritoneal cavity (PCI), lymph node involvement, and extra-abdominal metastasis. This staging system would be extremely useful for patients considered for the combined treatment modality, which is the only therapeutic option associated with a prolonged survival in this disease to date. The proposed TNM staging system should be validated in a prospective manner in the future.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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