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A Novel Nomogram for Peritoneal Mesothelioma Predicts Survival

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Abstract

Background—Malignant peritoneal mesothelioma (MPM) is a rare disease treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Estimation of personalized survival times can potentially guide treatment and surveillance.

Methods—We analyzed 104 patients who underwent CRS and cisplatin-based HIPEC for MPM. By means of 25 demographic, laboratory, operative, and histopathological variables, we developed

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a novel nomogram using machine-learned Bayesian belief networks with stepwise training, testing, and cross-validation.

Results—The mean peritoneal carcinomatosis index (PCI) was 15, and 66 % of patients had a completeness of cytoreduction (CC) score of 0 or 1. Eighty-seven percent of patients had epithelioid histology. The median follow-up time was 49 (1–195) months. The 3- and 5-year overall survivals (OS) were 58 and 46 %, respectively. The histological subtype, pre-CRS PCI, and preoperative serum CA-125 had the greatest impact on OS and were included in the nomogram. The mean areas under the receiver operating characteristic curve for the 10-fold cross-validation of the 3- and 5-year models were 0.77 and 0.74, respectively. The graphical calculator or nomogram uses color coding to assist the clinician in quickly estimating individualized patient-specific survival before surgery.

Conclusions—Machine-learned Bayesian belief network analysis generated a novel nomogram predicting 3- and 5-year OS in patients treated with CRS and HIPEC for MPM. Pre-CRS estimation of survival times may potentially individualize patient care by influencing the use of systemic therapy and frequency of diagnostic imaging, and might prevent CRS in patients unlikely to achieve favorable outcomes despite surgical intervention.

Malignant peritoneal mesothelioma (MPM) is a rare disease, with an estimated 400 new cases per year in the United States.¹ MPM arises within the abdominal serosa and forms nodular plaques on peritoneal surfaces. Patients typically present with abdominal distention, pain, or weight loss.² The disease may spread to the pleura, but distant metastases are rare.³ Intraperitoneal disease progression inevitably leads to small bowel obstruction, cachexia, and death in nearly all patients.⁴

Early therapies with palliative surgery or chemotherapy resulted in median overall survival (OS) of 6–12 months.^{4–6} Currently, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have emerged as standard treatments for patients with MPM.⁷ This strategy relies on maximal operative tumor debulking to improve efficacy of HIPEC, as the penetration of HIPEC into peritoneal nodules is generally limited to 3 mm.^{8,9} Patients are selected for CRS/HIPEC on the basis of their morbidity profile, functional status, and volume of disease. CRS/HIPEC for MPM results in 3-year OS of 46–67 % and a 5-year OS of 36–50 %, and it carries reported perioperative morbidity and mortality rates of 15–31 and 0–7 %, respectively.^{10–13}

Prior studies examined prognostic factors in an effort to improve the selection of patients who may benefit from CRS/HIPEC. Epithelioid subtype, absence of lymph node metastasis, CC score of 0/1, and receipt of HIPEC were prognostic factors associated with improved survival in a multi-institutional report of 404 patients with MPM (372 patients received CRS/HIPEC).¹² Other studies demonstrated improved outcome on the basis of low pre-CRS peritoneal carcinomatosis index (PCI), female gender, and age less than 60.^{2,14} Despite the identification of prognostic factors for patients with MPM treated with CRS/HIPEC, no clinical or molecular tools exist to predict personalized survival times before considered treatment with CRS/HIPEC and/or systemic chemotherapy. Commonly, clinical assessment tools are generated by multivariate analyses based on Cox proportional hazard models.

Clinical oncology is replete with such models, such as the Gail Breast Cancer Risk Assessment Tool.¹⁵

We selected a different approach: a Bayesian belief network (BBN). BBN modeling uses machine-learning algorithms to quickly evaluate potential network structures, selecting an optimal network according to criteria of parsimony and Shannon's mutual information.¹⁶ This approach avoids overfitting, does not rely on assumptions about the independence of covariates, and is robust against missing data. BBN models have been used increasingly in oncological outcomes research, e.g., the modeling of treatment and screening on breast cancer mortality and the modeling of drug combinations in the treatment of lymphoma.^{17,18}

Clinicians who treat patients with MPM face three cardinal questions: who will benefit from CRS/HIPEC, who should receive adjuvant chemotherapy, and how should patients be followed after CRS/HIPEC? We hypothesized that a first step to answer these questions requires a tool that can provide patient-specific survival times that are based on preoperative prognostic factors. Therefore, our goals included the creation of risk prediction models for 3- and 5-year OS, and the development of a user-friendly clinical assessment tool that would allow physicians to quickly estimate survival from easily acquired input values.

PATIENTS AND METHODS

Records were compiled from retrospective analysis of a prospectively maintained database of 104 patients with histologically proven MPM who underwent CRS/HIPEC between 1994 and 2010. All patients were enrolled in institutional review board–approved protocols at the National Cancer Institute. Patients with good functional status were eligible for CRS/HIPEC if preoperative CT scans revealed resectable disease localized to the abdominal cavity. The pre- and postoperative volume and extent of disease was analyzed by at least two of the validated tools including the Gilly score, PCI, CC score, and Bartlett index. The Gilly score includes the following stages: no lesions, localized lesions <5 mm, diffuse lesions <5 mm, lesions 5 mm to 2 cm, and lesions >2 cm. The PCI uses lesion size (0–3) and tumor distribution (0–12) to determine extent of disease (0–39).¹⁹ The CC score records residual disease after CRS: CC0 (no disease), CC1 (disease <0.25 cm), CC2 (disease 0.25–2.5 cm), and CC3 (disease >2.5 cm).¹⁹ The Bartlett index describes the amount of disease after CRS: no residual disease, <100 lesions and all <5 mm, >100 lesions or any >5 mm, and lesions >1 cm. For patients treated before the advent of the PCI and Gilly score, we converted operative reports, Bartlett index, and protocol-related documents to define the PCI for each patient (validated independently by two clinicians).

Histological subtypes were defined according to two grading systems and were reviewed by two independent pathologists. The first system used the World Health Organization (WHO) classification, which describes epithelioid, sarcomatoid, and biphasic subtypes.²⁰ The second system used three detailed categories: epithelioid with ≥10 % solid component, epithelioid with <10 % solid component, and a combined sarcomatoid/biphasic group.²¹

Surgery was performed with the goal of maximal cyto-reduction. All visible lesions were resected when possible, and en-bloc organ resections were performed on the basis of the

extent of disease. Peritoneotomies were performed to remove visible disease, and electrofulguration was performed on isolated small implants. HIPEC was performed via the closed method with continuous agitation. Large-bore in-and-out flow catheters were placed in the pelvis and above the liver. Perfusion was performed with cisplatin (250–450 mg/m²) at 40–42 °C for 90 minutes at a rate of 2 L/min. Appropriate drains and/or dwell catheters for early postoperative intraperitoneal chemotherapy (EPIC) were placed before final abdominal closure.

After surgery, 69 patients received EPIC with Taxol and 5-fluorouracil (5-FU). Single doses of Taxol (125 mg/m²) and 5-FU (800 mg/m²) were infused via an intra-abdominal dwell catheter on postoperative days 7–12. Patients were followed every 3 months with physical examination, laboratory assessments, and CT scans. Patients whose disease progressed were evaluated for repeat CRS/HIPEC or were referred for medical oncology consultation.

We trained machine-learned BBNs (ml-BBN) using commercially available machine-learning algorithms (FasterAnalytics, DecisionQ Corporation, Washington, DC). After data curation, stepwise training was undertaken to develop ml-BBN models for cross-validation. The iterative process consisted of recursive modeling, data curation, and selection of an appropriate cohort of data features intended to maximize ml-BBN model robustness. We trained the network to focus on posterior estimates of 3- and 5-year OS given known demographic, pathological, and serum tumor marker information.

Preliminary modeling was performed on the following potential prognostic factors: sex, age, Eastern Cooperative Oncology Group (ECOG) performance, smoking history, alcohol history, previous CRS, preoperative ascites, pre- and post-CRS PCI, pre- and post-CRS Gilly score, CC score, Bartlett index, surgery year (i.e., early vs. later experience as a continuous variable), receipt of EPIC, and receipt of second CRS/HIPEC procedure. Additional factors included pre- and postoperative CA-125 (within 3 months after surgery), the difference between pre- and postoperative CA-125, desmoplasia, mitotic rate, deep invasion, p53 staining, and p27 staining. The two histological grading systems were also modeled.

To assess model robustness and accuracy, we performed 10-fold train-and-test cross-validation using the final ml-BBN model by randomizing the data into 10 unique training sets. The training sets contained 90 % of the data. Ten unique corresponding test sets were developed containing the remaining 10 % of the data. Once each test model was created with a training set, the matching test set was entered into the BBN model. This process generated patient-specific estimates for each record for independent variables of interest. A receiver operating characteristic (ROC) curve was plotted for each test. Area under the ROC curve (AUC) was then calculated, which served as a metric of overall model accuracy and robustness for 3- and 5-year OS.

RESULTS

Baseline characteristics for the 104 patients are summarized in Table 1. Treatment, pathology, and survival related data are summarized in Table 2. The median pre-CRS PCI was 15 (range 3–36), and 69 patients (66.3 %) had a CC score of 0/1. Sixty-nine patients

(66.3 %) received EPIC, and 11 patients (11.6 %) underwent repeat CRS/HIPEC. Eighty-seven percent of patients had epithelioid subtype, and 13 % had either sarcomatoid or biphasic subtype.

The median follow-up time was 49.4 (range 1–195) months. The 3- and 5-year OS were 58 and 46 %, respectively, with median OS of 52.0 (range 1–195) months. The 3- and 5-year progression-free survivals were 26 and 13 %, respectively, with median time to progression of 20.8 (range 1–81) months. The median OS for patients receiving EPIC and patients not receiving EPIC was 67 and 35 months, respectively ($p = 0.345$). The median OS for patients receiving a second CRS/HIPEC and patients not receiving a second CRS/HIPEC was 103 and 48 months, respectively ($p = 0.047$).

We demonstrate the initial unpruned ml-BBN for the 5-year OS model in Fig. 1. We generated similar ml-BBN models for the 3-year OS model. Initial model generation revealed several factors that lacked prognostic significance or that overlapped other factors. Three variables with the greatest influence on OS were pre-CRS PCI, preoperative serum CA-125, and detailed histological subtype. The pre-CRS PCI was more prognostic than the post-CRS PCI, pre- and post-CRS Gilly score, Bartlett index, and CC score. The preoperative CA-125 was more prognostic than the postoperative CA-125 or the difference between the pre- and postoperative CA-125. The detailed histological subtype was more prognostic than tumor desmoplasia or deep invasion.

The final ml-BBN model included pre-CRS PCI, pre-operative CA-125, and detailed histological subtype. We graphically demonstrate the final BBN for the 3-year and 5-year OS models in Fig. 2. The mean AUC for the 10-fold cross-validation of the 3-year model was 0.77. The mean AUC for the 10-fold cross-validation of the 5-year model was 0.74. The positive predictive value and negative predictive value of the 3-year model was 73.1 and 67.6 %, respectively. The positive predictive value and negative predictive value of the 5-year model was 73.9 and 73.3 %, respectively.

The graphical calculator or nomogram uses color coding to assist the clinician in quickly estimating individualized patient-specific OS (Fig. 3). The detailed histological subtype, pre-CRS PCI, and preoperative CA-125 were incorporated into the calculator. The pre-CRS PCI was binned into three categories: 10, 11–19, and >19. The preoperative CA-125 was binned into three categories: 17, 18–71, and >71 U/ml. The model is used by simply applying the three factors on the left to the corresponding color on the right to determine estimates of 3- and 5-year OS.

DISCUSSION

We undertook this study to help clinicians estimate individualized patient-specific OS for patients with MPM. We sought to develop a ml-BBN to identify prognostic factors in patients with MPM treated with CRS/HIPEC. We also sought to create a user-friendly clinical decision support tool that uses readily obtainable preoperative information to estimate 3- and 5-year OS in patients with this challenging disease. The machine-learned

methodology allowed the robust analysis of 25 factors using Bayesian classification to identify relationships between statistically significant independent covariates.

We found that pre-CRS PCI predicted outcome in our model, similar to other reports.^{12,13,22} Though some have suggested that CC score carries greater prognostic significance, we found pre-CRS PCI to be the most prognostic. Recently, Yan et al. proposed a novel tumor, node, and metastasis staging system based on review of 294 patients with diffuse MPM undergoing CRS/HIPEC.²² They defined T1 as PCI 0–10, T2 as PCI 11–20, T3 as PCI 21–30, and T4 as PCI 30–39. Similarly, our model identified three groups based on PCI: low risk with PCI ≤ 10, medium risk with PCI 11–19, and high risk with PCI >19. These studies suggest the strong influence of pre-CRS PCI on patient prognosis.

The role of CA-125 as a tumor marker in patients with MPM has not been fully elucidated.²³ A study assessing 46 patients undergoing CRS/HIPEC for MPM reported a preoperative diagnostic sensitivity of 53.4 % for CA-125. In a follow-up report, the authors described 82.0 % 5-year OS for patients with baseline CA-125 ≤ 35 U/ml and 42.1 % 5-year OS for patients with CA-125 >35 U/ml.²⁴ They suggested that CA-125 parallels tumor growth and regression after CRS/HIPEC and may be useful when measured serially.¹³ Rump et al. described a mechanism for binding between CA-125 and mesothelin, and they suggested that this mechanism may contribute to peritoneal dissemination by initiating cell attachment to the mesothelial epithelium.²⁵

The epithelioid subtype occurs in about 75 % of patients with MPM. Heterogeneity of the epithelioid subtype has led to identification of additional subgroups of MPM, including tubulopapillary, acinar, adenomatoid, and solid, and evidence suggests worse prognosis in patients with solid subtype.^{20,21} Our BBN model showed improved accuracy with the detailed histological subtype compared to the classic WHO classification. Recently, Kadota et al. reported worse prognosis in patients with pleomorphic epithelioid pleural mesothelioma, which they defined as epithelioid with >10 % pleomorphism.²⁶ Further work in this area may yield clues to the prognostic importance of the specific pathologic subtypes.

Our series included 69 patients who received EPIC with Taxol and 5-FU. Ninety-four of 372 patients in a multi-institutional review received EPIC (Taxol or cisplatin and doxorubicin) in addition to CRS/HIPEC.¹² In both studies, no statistically significant benefit was detected, raising questions about the benefit of EPIC. Sugarbaker et al. described improved survival in 17 patients undergoing second CRS (89 vs. 55 months, $p = 0.526$).¹¹ We report on 11 patients who received repeat CRS/HIPEC, with a difference in median OS of 103 versus 48 months ($p = 0.047$). The small numbers and inherent selection bias of those who would qualify for a second CRS/HIPEC prevent definitive conclusions. Candidate patients for second CRS/ HIPEC should be selected carefully.

The ml-BBN methodology offered certain advantages compared to logistic regression multivariate models. ml- BBNs integrate all data elements into one hierarchical structure similar to neural networks. Logistic regression models, on the other hand, use a linear construct to individually assess each outcome of interest. Although this latter approach may improve goodness of fit, it is not as robust a method as ml-BBN modeling, which provides

better accuracy of estimates when clinical records with missing data elements are used. Moreover, once constructed, ml-BBN can learn and improve with each additional patient record.

Our evaluation of patients with MPM has limitations. The lack of lymph node positivity among patients in our cohort prevented the inclusion of this factor in the modeling. However, lymph nodes metastasis is uncommon, only occurring in about 7 % of patients.^{12,22} Another limitation included the lack of standardization of preoperative and postoperative chemotherapy regimens. Finally, this investigation was performed in a retrospective fashion and should be validated in other data sets and in a prospective manner.

We propose that this clinical assessment tool may facilitate the determination of surgical candidacy for patients before exploratory laparotomy. Histological subtype can be determined by percutaneous needle biopsy or paracentesis with cytology, or at time of diagnostic laparoscopy. CA-125 requires a simple blood draw. Pre-CRS PCI can be estimated by CT or laparoscopy. Yan et al. described a system for estimating PCI based on preoperative CT scan findings, though there was no comparison between the CT estimate of PCI and the operative PCI in their report.²⁷ Laterza et al. described a laparoscopic PCI scoring in which they accurately predicted a CC score of 0/1 after CRS in 33 of 34 patients.²⁸

We have constructed the first clinical assessment tool (nomogram) to predict survival in patients treated with CRS/HIPEC for MPM. The tool provides a simple graphical display of survival based on clinical parameters readily obtainable before operation: histological subtype, CA-125, and pre-CRS PCI. Preoperative estimation of survival may individualize patient treatment and follow-up, such as influencing the extent of surgical and systemic therapy, and the frequency of diagnostic imaging. This model should be validated in other data sets and in a prospective manner, and future refinement will likely improve its predictive accuracy.

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FIG. 1.

Unpruned BBN for the 5-year model demonstrating associations between factors included in the initial model. Each box represents a variable in the initial model and contains variable subcategories in the *left column* and subcategory counts in the *right column*. Several factors, such as age at treatment, Eastern Cooperative Oncology Group performance status, and mitotic rate were not associated with survival. Factors such as CC score and pre-CRS PCI were codependent with other factors and were associated with mortality

FIG. 2. Final BBN models showing 3- and 5-year overall survivals. Preoperative CA-125, PCI before CRS, and histological subtype were most associated with survival in both models

FIG. 3. Clinical assessment tool incorporating detailed histological subtype, preoperative CA-125, and PCI to estimate 3- and 5-year overall survival. The 3 factors on the left are applied to the corresponding color on the right to determine estimates of survival

TABLE 1

Summary of baseline characteristics for 104 patients with malignant peritoneal mesothelioma

Characteristic	Value
Age, y	50.9 (16–79)
Sex, male	61 (58.7 %)
Smoking history	42 (40.4 %)
Alcohol history	40 (38.5 %)
ECOG 0	90 (86.5 %)
Previous CRS	26 (25 %)
Preoperative ascites	61 (58.7 %)

Data are presented as median (range) and *n* (%)*ECOG* Eastern Cooperative Oncology Group, *CRS* cytoreductive surgery

TABLE 2

Clinicopathologic data for 104 patients with malignant peritoneal mesothelioma

Characteristic	Value
CA-125, U/ml	
Before surgery	53.0 (1.3–12,564)
After surgery	32.3 (1.4–4,610)
Peritoneal cancer index	
Before surgery	15 (3–36)
After surgery	4 (0–35)
Gilly score	
Before surgery	3 (2–4)
After surgery	1 (0–4)
Cytoreduction score 0/1	69 (66.3 %)
EPIC	69 (66.3 %)
Epithelioid histology	86.5 %
Desmoplasia	78/99 (78.8 %)
Deep invasion	81/99 (81.2 %)
Mitotic rate	2 (0–10)
p53 stain <5 %	78/92 (84.8 %)
p27 stain >75 %	42/92 (45.7 %)

Data are presented as median (range) and *n* (%)*EPIC* early postoperative intraperitoneal chemotherapy