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Using Machine Learning to Construct Nomograms for Patients with Metastatic Colon Cancer

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Abstract

Aim: Patients with synchronous colon cancer metastases have highly variable overall survival (OS), making accurate predictive models challenging to build. We aim to use machine learning to more accurately predict OS in these patients and to present this predictive model in the form of nomograms for patients and clinicians.

Methods: Using the National Cancer Database (2010-2014), we identified right colon (RC) and left colon (LC) cancer patients with synchronous metastases. Each primary site was split into training and testing datasets. Nomograms predicting 3-year overall survival were created for each site using Cox proportional hazard regression with lasso regression. Each model was evaluated by both calibration (comparison of predicted versus observed overall survival) and validation (degree of concordance as measured by c-index) methodologies.

Results: A total of 11,018 RC and 8,346 LC patients were used to construct and validate the nomograms. After stratifying each model into 5 risk groups, the predicted OS was within the 95% CI of the observed OS in 4 out of 5 risk groups for both the RC and LC models. Externally validated c-indexes at 3 years for RC and LC models were 0.794 and 0.761, respectively.

Conclusions: Utilization of machine learning can result in more accurate predictive models for patients with metastatic colon cancer. Nomograms built from these models can assist clinicians and patients in the shared decision-making process of their cancer care.

INTRODUCTION

Colorectal cancer is the fourth most common cancer diagnosis in the United States, with an estimated 140,000 new diagnoses and 50,000 deaths annually (1). Of the newly diagnosed patients, approximately 20-30% will present with metastatic disease (2,3). Classically,

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metastatic disease has been considered incurable and associated with poor overall survival (1). However, with advances in chemotherapy and shifting paradigms in the definition of resectable metastases, overall survival has improved in recent years (4–7).

Previous attempts have been made to build accurate predictive models in order to assist clinicians and patients with prognostic information and care-planning. The most commonly used measure to evaluate the performance of predictive models is the concordance index (c-index), which estimates the probability of concordance between predicted and observed outcomes (8). A perfect concordance is 1.0, while 0.50 is equatable to a coin-flip. Achieving accurate predictions in this patient population has been challenging, with most models having c-indexes <0.70 (9–11). In addition, previous models have often been limited to a single metastatic organ, most often liver or lung (9,10,12–16). This is problematic because many patients present with multiple metastatic sites. For example, more than 50% of patients with liver metastasis have another metastatic site (3). Attempts to model the survival for patients with different metastatic disease locations perform even worse, with c-indexes <0.65 (17). The poor performance of these models may be because outcomes in patients with metastatic disease are highly variable due to the wide variety of clinical conditions (18). In addition, there is mounting evidence that colon and rectal metastases are distinct entities, with different metastatic patterns and outcomes (2,3,19). Therefore, it may be prudent to build a colon- or rectum-specific predictive model. Furthermore, for patients with colon cancer, there is mounting evidence for differences in overall survival based on laterality of colon cancer (3,19–23). Because of this, it may be prudent to develop models based on the laterality of the primary colon tumour as well.

Previous models have been built on simple multivariable regression techniques, using either logistic regression or Cox proportional hazard modeling (9–17). However, advanced predictive modeling using machine learning can be used to build models that are more accurate, robust, and generalizable (24). Briefly, machine learning algorithms can be used to create predictive models by "learning" from large data sets. It is especially helpful in predictive modeling as it can identify relevant predictors based on its previously "learned" experience. While still in its infancy, especially in surgical applications, the use of machine learning has slowly infiltrated clinical practice (25–30).

In this study, our aim was to construct a predictive nomogram for 3-year overall survival in patients with metastatic colon cancer using machine learning techniques and to present our models in the form of user-friendly and approachable nomograms.

METHODS

Patient Sample and Variables

Patients were identified in the National Cancer Database (NCDB) (31), a national oncology outcomes database that is jointly sponsored by the American College of Surgeons' Commissions on Cancer (CoC) and the American Cancer Society. It contains clinical oncology data sourced from over 1,500 CoC-accredited centers and represents >70% of newly diagnosed cancer cases nationwide. Because the NCDB only contains de-identified patient information, this study was exempt from Institution Review Board approval.

Using the NCDB, all patients with metastatic colon adenocarcinoma diagnosed from 2010 to 2014 were identified. Patients with non-metastatic disease were excluded. The primary tumour was identified as adenocarcinoma by International Classification of Disease for Oncology histology codes (8140-8145, 8210, 8211, 8220, 8221, 8255, 8261-8263, 8310, 8323, 8330-8332, 8480, 8481, 8490, 8525, 8530, 8570-8574). Patients were split into separate cohorts based on the laterality of the primary tumor. The right colon (RC) was defined as caecum to transverse colon, and the left colon (LC) was defined as splenic flexure to sigmoid colon. Patients with overlapping tumors and non-otherwise-specified locations were excluded from analysis.

Variables were selected due to clinical significance and availability within the NCDB. From the NCDB, patient age, Charlson-Deyo Comorbidity Score, and tumour grade were collected. The CEA level, defined in the NCDB as the highest pre-treatment CEA level, was split into approximate quartiles within the NCDB (6ng/mL, 6.1-28.9ng/mL, 29-97.9ng/mL, and 98ng/mL). Tumour size was categorized into 0.1=1cm, 1.1-2cm, 3.1-4cm, 4.1-5cm, 5.1-6cm, 6.1-7cm, and >7cm. Metastasis at the time of diagnosis to the liver, lung, brain, bone, and peritoneum were identified and reported as binary variables (i.e. yes/no). Resection of the primary tumor site and of a metastatic site (excluding resection of only distant lymph nodes) was also dichotomized. The number of positive lymph nodes was reported as a continuous variable, with aspiration of positive lymph nodes and unknown number of positive lymph nodes considered as one positive lymph node. Chemotherapy was dichotomized into no chemotherapy versus any type of chemotherapy (including neoadjuvant and adjuvant therapy). For all variables, patients with unknown data points were excluded from analysis.

Nomogram Construction and Validation

The RC and LC cohorts were split into a training set (diagnosis year 2010-2012) and testing set (2013-2014). All patients with missing data were removed from analysis. Differences between the training set and testing set were evaluated using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Kaplan-Meier analysis with log-rank testing was used to compare the overall survival (OS) between the datasets.

Separate nomograms were created for RC and LC. The nomograms were created using a 10-fold cross-validated Cox proportional hazard regression with lasso regression. The lasso (least absolute shrinkage and selection operator) is a machine-learning technique which performs both variable selection (which reduces the number of predictors so that non-significant predictors are removed from the final model) and regularization (which decreases each predictors' ability to affect the predicted outcome) (32). By performing both variable selection and regularization, the lasso is able to build accurate models without under-fitting or over-fitting the training data, leading to accurate models that are also generalizable. For our analysis, we combined properties of the lasso with Cox proportional hazard analysis, in which predictors for overall survival was subject to selection and regularization. For both nomograms, the predictive outcome was the probability of overall survival at 3 years.

We examined the performance of our predictive models by both calibration (external only) and validation (internal and external), as described previously in our analysis of patients with metastatic rectal cancer (33). In external calibration, we stratified the test dataset into 5 risk groups by probability of OS and report the predicted versus actual probability of OS at 3 years for each risk group. In internal and external validation, we report the time-dependent c-indexes at 1, 2, and 3 years.

To justify splitting the datasets by laterality, we performed a pooled cohort analysis, which included patients with both right and left colon primary tumour sites. In this analysis, the location of the primary tumour was used as a predictor within the model. Internal/external validation and external calibration was performed on this pooled cohort as described above.

All statistical and machine-learning analyses were performed using R (Version 3.3.2, R Foundation, Vienna, Austria) and R package *hdnom* (34). The level of significance was set at 0.05 and all comparisons are two-tailed.

RESULTS

Of the 761,528 patients in the NCDB colon cancer dataset, 53,107 patients were identified with synchronous metastatic disease. After exclusion, a total of 19,324 patients were included in our analysis. Of these, 6,432 patients with right colon cancer and 4,918 patients with left colon cancer were included in the training dataset. A total of 4,586 patients with right colon cancer and 3,428 patients with left colon cancer were included in the testing dataset. A comparison of the training and testing cohorts for the RC and LC cohorts are shown in Tables 1. Figure 1 shows the Kaplan-Meier survival curve for RC (a) and LC (b) patients. For the RC cohort, the median OS for the training group (15.8 months, 95% CI 15.1 – 16.3) was significantly shorter compared to the testing group (17.2 months, 95% CI 16.5 – 17.9, p=0.007). For the LC cohort, there was no significant difference in median OS between the training group (26.0 months, 95% CI 25.1 – 27.0) and the testing group (27.7 months, 26.6 – 29.1, p=0.165).

Figure 2 shows the nomogram for patients with primary metastatic RC (a) and LC (b). For each nomogram, predictors are assigned a range of points that, when totaled, will equate to a given predicted probability of overall survival at 3 years. External calibration, stratified into 5 risk-groups, is shown in Table 2. On external calibration, there was no significant difference in the predicted 3-year OS from the RC and LC model compared to the actual 3-year OS in the test dataset in 4 out of 5 risk groups. For the risk group that was significantly different, the model under-predicted the 3-year OS in both the RC and LC cohorts (Table 2). For the RC cohort, the time-dependent internal validation c-indexes at 1, 2, and 3 years were 0.792 (95% CI 0.789 – 0.795), 0.768 (95% CI 0.765 – 0.771), and 0.754 (95% CI 0.749 – 0.757), respectively (Table 3). The external validation c-indexes for the RC cohort at 1, 2, and 3 years were 0.804, 0.775, and 0.794, respectively. For the LC cohort, the time-dependent internal validation c-indexes at 1, 2, and 3 years were 0.821 (95% CI 0.818 – 0.824), 0.782 (95% CI 0.781 – 0.785), and 0.768 (95% CI 0.766 – 0.771), respectively (Table 3). The external validation c-indexes for the LC cohort at 1, 2, and 3 years were 0.801, 0.774, and 0.761, respectively.

For the pooled cohort, the internal (1, 2, 3 years: 0.809, 0.782, 0.767) and external (1, 2, 3 years: 0.802, 0.771, 0.790) validation resulted in similar c-indexes to the unpooled models (Table 3). However, on external calibration, the pooled cohort performed slightly worse than the individual models, with 2 out of 5 risk groups having significant differences in the predicted 3-year OS compared to the actual 3-year OS (Table 2).

DISCUSSION

Patients with metastatic colon cancer have high variability in overall survival, making accurate predictive models challenging. However, by using a large nationwide oncology database, and harnessing the predictive power of machine learning, we were able to construct nomograms predicting the probability of 3-year OS in metastatic colon cancer patients with superior accuracy to those previously published (9–11,17).

The performance of previous predictive models for patients with metastatic colon cancer has been limited by c-index <0.70 (9–17). These models have relied on multivariable regression techniques for predictive modeling. Machine learning techniques, such as the lasso used in this study, has been shown to improve predictive accuracy (24,28). In addition, previous models often did not separate colon cancer from rectal cancer and did not separate colon cancer based on laterality. We chose to build separate models based on laterality because there is a growing body of literature to suggest that right and left colon cancers have large variations in overall survival (2,19,21–23). This suggests right and left colon cancers should be considered as distinct entities and building separate models may improve predictive accuracy. We tested this hypothesis by creating a pooled model that included all metastatic colon cancer patients. While the internal and external validation of the pooled model was comparable to the laterality-specific models, the external calibration of the pooled model performed worse. This supports the need to create separate predictive models based on the laterality of the primary colon cancer.

In addition, the number of points that each predictor contributed to the predicted overall survival also varied by laterality. The number of points is determined by the lasso algorithm and is based on the predictors' contribution to OS. For example, bone, lung, and brain metastases accounted for more points in the LC nomogram compared to the RC nomogram. This difference may be explained by the fact that patients with RC cancer tend to have poorer prognosis due to inherent tumour biology (19,21,22), and the contribution of metastatic sites to OS is lower in RC cancer than in LC cancer. Of the categorical variables in the RC nomogram, lung metastasis and brain metastasis had the fewest allocated points among all predictors, which would suggest that their contribution to OS is low. While brain metastases has been associated with very poor prognosis (35,36), it also often occurs late in the disease course, when multiple metastases and other comorbidities may also contribute to the poor survival in these patients. In this way, other predictors may "crowd out" the effect brain metastasis has on OS. Similarly, while pulmonary metastases represent the second most common metastatic site, care for these patients have improved so dramatically that previous studies have shown no effect of pulmonary metastases on OS in patients with metastatic disease (17,23,37).

By stratifying the external calibration into 5 risk groups, we were able to assess the predictive accuracy of each model. In both the RC and LC cohorts, the model significantly under-predicted the probability of survival in patients with the highest risk (worst probability of survival at 3 years). This suggests that there are likely unmeasured variables (i.e. patient comorbidities, surgical complications) that are contributing to OS in these high-risk patients, leading the model to under-predict survival for these patients. Future work will concentrate on improving the predictive model for this group of patients.

The use of machine learning can also help build effective nomograms. Nomograms, which are graphical representations of complex mathematical formulas, are popular because they are user-friendly and approachable to both clinicians and patients. This is especially important in oncology, as they can be a helpful tool in the shared decision-making process that is key in oncology care (38–40). However, nomograms can become too complex and cumbersome when there are too many predictors. In this case, the lasso algorithm allowed us to drop "unimportant" predictors while maintaining predictive accuracy, making our nomograms both accessible and accurate. These machine learning models can also continue to "learn" and improve their accuracy with more data points. Therefore, as more data becomes available, these models will become more accurate. In addition, future research will focus on testing other machine learning algorithms that may produce superior results than the lasso.

It is our hope that these nomograms can be used to set expectations for patients and clinicians. For example, using our nomogram, a 70 year-old patient with poorly-differentiated right colon cancer, pre-operative CEA of 7.0ng/mL, synchronous liver metastasis without metastasectomy, resected 3.5cm primary tumor with 5 positive lymph nodes, and who is undergoing systemic therapy, would accrue 90 points. This equates to a predicted 3-year OS of approximately 30%. However, if that patient underwent metastasectomy, their predicted 3-year OS would be closer to 40%. Conversely, if the patient does not undergo systemic therapy, their predicted 3-year OS is less than 5%. In this way, these nomograms may have a potential role in the shared decision-making process between patients and clinicians.

Limitations

The predictive models were constructed using data from a retrospective nationwide database. While this provided large training and testing datasets, it limited the predictors that can be used to construct the model. For example, the NCDB does not contain details regarding the specific chemotherapy regimens used to treat patients, nor does it contain details on the timing of metastasectomy. In addition, the NCDB only includes metastases to the liver, lung, brain, bone, or peritoneum. While previous studies have shown that >90% of patients with metastatic disease have metastases to these sites (2), the use of these nomograms in patients who present with rarer sites of metastasis may be limited. The NCDB only records metastatic sites at the time of diagnosis, so these nomograms are limited to patients who present with synchronous metastatic disease. Our analysis was limited from 2010 because that was the first year metastatic data became available in the NCDB. Because the testing dataset included patients diagnosed in 2013, we were limited to 3-year overall survival. This

is not uncommon in analysis of metastatic colon cancer (9,10,41). In the NCDB, 3-year OS for these patients is approximately 25%, highlighting the deadly nature of this disease. Though we split our dataset into distinct training and testing datasets, the optimal method to externally validate our models is to use a separate dataset. However, because the NCDB covers >70% of cancer diagnoses in the United States, it may be challenging to find patients that are not already represented in the NCDB. A potential solution is to prospectively collect data, though this is time-consuming and potentially unfeasible. The nomograms are split by the location of the primary tumour, which may limit its use in patients whose primary tumour location is unknown or have multiple primary tumours in different locations. There were not enough patients with overlapping and unknown tumour locations in the NCDB to validate the model on these patients. The NCDB contains data only from CoC-accredited centers. The outcomes of patients at these institutions may be different than those treated at non-CoC-accredited centers, limiting generalizability. Lastly, the machine-learning models used in this analysis required complete data for analysis. Therefore, patients with missing data were excluded. We attempted to minimize the number of patients that were excluded by using clinically significant variables with low amounts of missing data. While a large number of patients were excluded, we were still able to maintain a large sample size that was further bolstered by 10-fold cross-validation during model construction.

Conclusions

To our knowledge, this is the first application of machine learning nomograms to predict survival in patients with metastatic colon cancer. These models have superior performance compared to the previous predictive models, showcasing the advantages of machine learning techniques. While nomograms are already easily accessible to patients and clinicians, the models used to build these nomograms can easily be transformed into other media (e.g. smartphone app) and future efforts will concentrate on dissemination of these models. Nonetheless, the nomograms created in this study can be especially useful in the shared decision-making process between clinicians and patients with metastatic colon cancer.

ACKNOWLEDGEMENTS

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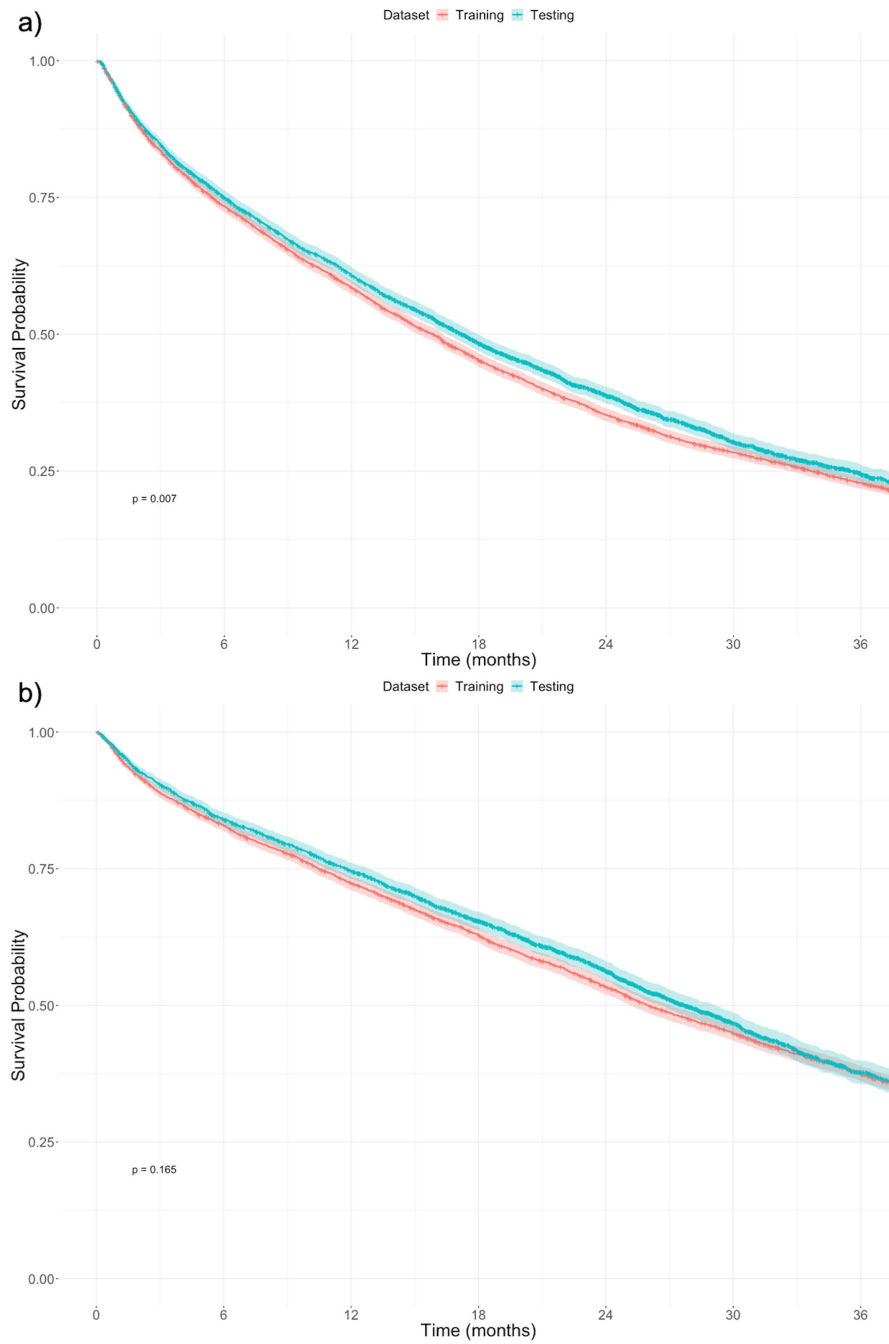
STATEMENT

Patients with metastatic colon cancer have highly variable survival, making it difficult to build accurate predictive models. Machine learning can be used to make more accurate predictive models that can help patients and clinicians in setting expectations and planning potential treatment options.

Figure 1.
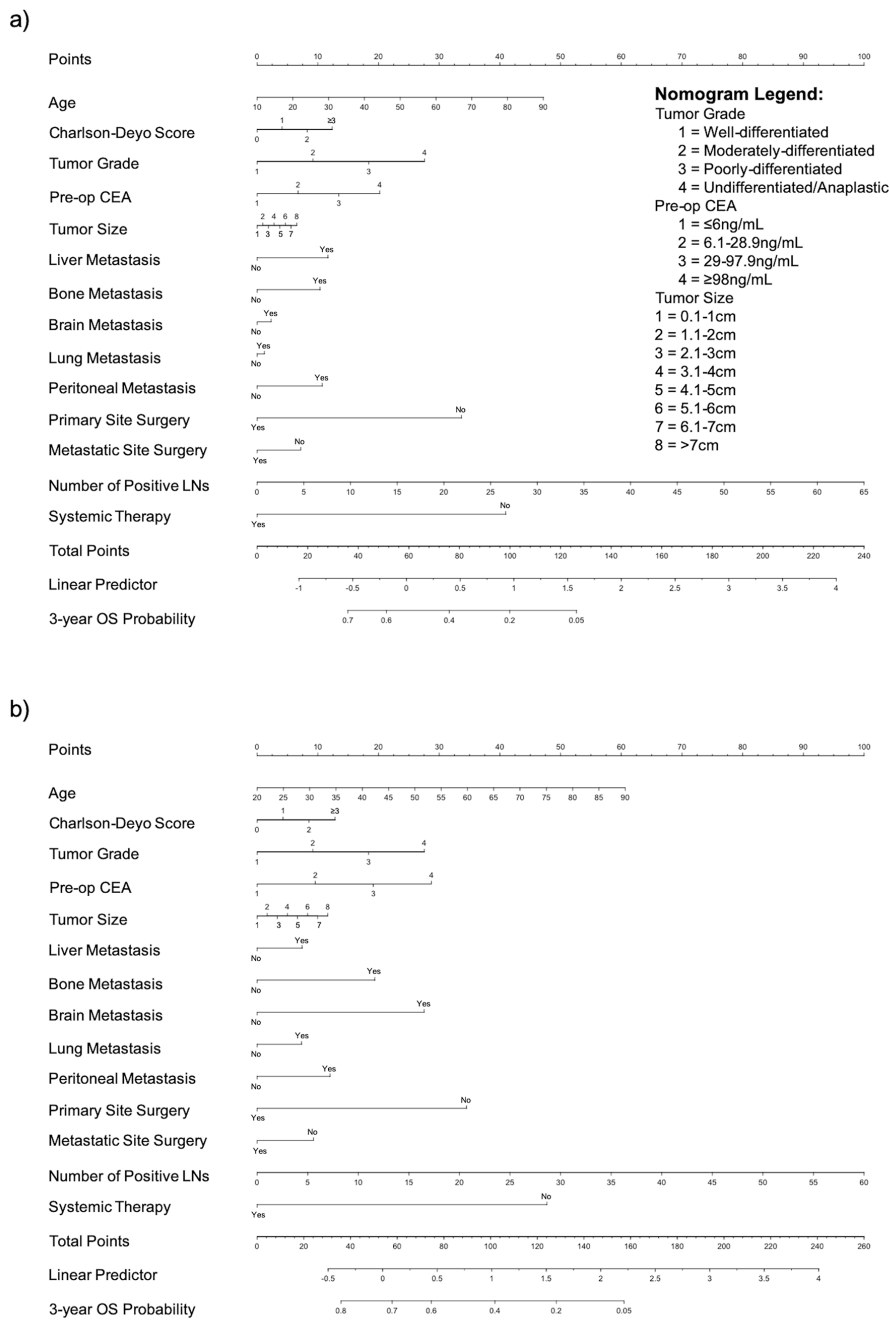Kaplan-Meier curves comparing the training and testing datasets for the right colon (a) and left colon (b) cohorts.

a)

b)

Figure 2.
Nomograms predicting the 3-year overall survival for patients with metastatic right colon (a) and left colon (b) cancers.

Table 1.

Comparison of the training and testing datasets for right and left colon cancer patients.

	Right Colon			Left Colon		
	Training	**Testing**	**p-value**	**Training**	**Testing**	**p-value**
Total # Patients	6432	4586	-	4918	3428	-
Median Age (range)	67 (18 – 90)	67 (18 – 90)	0.851	61 (20 – 90)	60 (18 – 90)	0.002[*]
Charlson-Deyo Score			0.689			0.805
0	4501 (70.0%)	3228 (70.4%)		3675 (74.7%)	2559 (74.6%)	
1	1434 (22.3%)	1025 (22.4%)		951 (19.4%)	674 (19.7%)	
2	359 (5.6%)	232 (5.1%)		215 (4.4%)	137 (4.0%)	
3	138 (2.1%)	101 (2.2%)		77 (1.6%)	58 (1.7%)	
Grade Differentiation			0.214			0.474
Well	328 (5.1%)	213 (4.6%)		312 (6.3%)	226 (6.6%)	
Moderate	3824 (59.5%)	2791 (60.9%)		3546 (72.1%)	2467 (72.0%)	
Poor	1929 (30.0%)	1363 (29.7%)		913 (18.6%)	614 (17.9%)	
Undifferentiated	351 (5.5%)	219 (4.8%)		147 (3.0%)	121 (3.5%)	
Highest CEA Level			<0.001[*]			<0.001[*]
6ng/mL	1966 (30.6%)	1497 (32.6%)		1281 (26.0%)	913 (26.6%)	
6.1-28.9ng/mL	1727 (26.9%)	1157 (25.2%)		1333 (27.1%)	882 (25.7%)	
29-97.9ng/mL	1265 (19.7%)	746 (16.3%)		1007 (20.5%)	598 (17.4%)	
98ng/mL	1474 (22.9%)	1186 (25.9%)		1297 (26.4%)	1035 (30.2%)	
Tumor Size			0.646			0.091
0.1-1cm	77 (1.2%)	48 (1.0%)		62 (1.3%)	45 (1.3%)	
1.1-2cm	209 (3.2%)	125 (2.7%)		211 (4.3%)	125 (3.6%)	
2.1-3cm	618 (9.6%)	457 (10.0%)		590 (12.0%)	438 (12.8%)	
3.1-4cm	1154 (17.9%)	789 (17.2%)		1007 (20.5%)	656 (19.1%)	
4.1-5cm	1354 (21.1%)	988 (21.5%)		1119 (22.8%)	725 (21.1%)	
5.1-6cm	1054 (16.4%)	740 (16.1%)		757 (15.4%)	571 (16.7%)	
6.1-7cm	723 (11.2%)	530 (11.6%)		468 (9.5%)	367 (10.7%)	
>7cm	1243 (19.3%)	909 (19.8%)		704 (14.3%)	501 (14.6%)	
Liver Metastasis	5328 (82.8%)	3753 (81.8%)	0.174	4211 (85.6%)	2917 (85.1%)	0.499
Bone Metastasis	245 (3.8%)	163 (3.6%)	0.485	159 (3.2%)	116 (3.4%)	0.704
Brain Metastasis	91 (1.4%)	51 (1.1%)	0.165	43 (0.9%)	33 (1.0%)	0.676
Lung Metastasis	1129 (17.6%)	853 (18.6%)	0.158	974 (19.8%)	709 (20.7%)	0.326
Peritoneal Metastasis	2141 (33.3%)	1532 (33.4%)	0.896	1411 (28.7%)	949 (27.7%)	0.315
Primary Site Resected	5606 (87.2%)	3839 (83.7%)	<0.001[*]	4215 (85.7%)	2829 (82.5%)	<0.001[*]
Metastatic Site Resected	1718 (26.7%)	1217 (26.5%)	0.840	1334 (27.1%)	935 (27.3%)	0.879
Median # of Positive LNs (range)	3 (0 – 61)	3 (0 – 62)	<0.001[*]	2 (0 – 58)	2 (0 – 83)	<0.001[*]
Received Chemotherapy	4524 (70.3%)	3324 (72.5%)	0.014[*]	3813 (77.5%)	2764 (80.6%)	<0.001[*]

[*] Significant p-value

Table 2.

External calibration showing probability of 3-year OS for all cohorts

	Right Colon		Left Colon		Pooled Analysis	
Risk Group	**Observed (95% CI)**	**Predicted**	**Observed (95% CI)**	**Predicted**	**Observed (95% CI)**	**Predicted**
1 (Highest Risk)	0.043 (0.029 – 0.064)	0.007[†]	0.116 (0.088 – 0.152)	0.045[†]	0.045 (0.034 – 0.059)	0.007[†]
2	0.104 (0.080 – 0.136)	0.081	0.254 (0.215 – 0.300)	0.228	0.105 (0.088 – 0.127)	0.080[†]
3	0.216 (0.183 – 0.255)	0.209	0.335 (0.287 – 0.391)	0.389	0.207 (0.183 – 0.234)	0.211
4	0.345 (0.306 – 0.389)	0.340	0.500 (0.454 – 0.552)	0.522	0.352 (0.324 – 0.382)	0.350
5 (Lowest Risk)	0.499 (0.459 – 0.543)	0.482	0.662 (0.616 – 0.712)	0.652	0.499 (0.470 – 0.529)	0.496

[†]Outside of 95% CI of observed probability

Table 3.

Time-dependent internal and external validation the right colon cohort, left colon cohort, pooled cohort, and cross-fit cohort analyses.

	Right Colon		Left Colon		Pooled Analysis	
Year	Internal (95% CI)	External	Internal (95% CI)	External	Internal (95% CI)	External
1	0.792 (0.789 – 0.795)	0.804	0.821 (0.818 – 0.824)	0.801	0.809 (0.806 – 0.811)	0.802
2	0.768 (0.765 – 0.771)	0.775	0.782 (0.781 – 0.785)	0.774	0.782 (0.779 – 0.784)	0.771
3	0.754 (0.749 – 0.757)	0.794	0.768 (0.766 – 0.771)	0.761	0.767 (0.764 – 0.770)	0.790