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TITLE: Personalising survival predictions in advanced colorectal cancer: the ARCAD nomogram project

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This work is dedicated to Daniel J. Sargent (deceased September 2016)

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Previously presented:

Earlier versions of this work were presented in poster format at the GI cancers symposium and ASCO annual meeting in 2015:

Sjoquist KM, Renfro LA, Simes J, et al: Nomograms for overall survival (OS) and progression-free survival (PFS) in metastatic colorectal cancer (metastatic colorectal carcinoma): Construction from 19,678 ARCAD patients. ASCO Meeting Abstracts 33:659, 2015

Sjoquist KM, Bokemeyer C, Renfro LA, et al: Calculators for overall survival (OS) and progression-free survival (PFS) in metastatic colorectal cancer (metastatic colorectal carcinoma): Construction from 19,678 ARCAD patients. ASCO Meeting Abstracts 33:3555, 2015

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Supplementary appendix: 1 table

Abstract

Background

Estimating prognosis on the basis of clinicopathologic factors can inform clinical practice and improve risk stratification for clinical trials. We constructed prognostic nomograms for overall survival and progression-free survival in metastatic colorectal carcinoma by using the ARCAD database.

Methods

Data from 22,674 patients in 26 randomized phase III clinical trials since 1997 were used to construct and validate Cox models, stratified by treatment arm within each study. Candidate variables included baseline age, sex, body mass index, performance status, colon vs. rectal cancer, prior chemotherapy, number and location of metastatic sites, tumor mutation status (BRAF, KRAS), bilirubin, albumin, white blood cell count, hemoglobin, platelets, absolute neutrophil count, and derived neutrophil-to-lymphocyte ratio. Missing data (<11%) were imputed, continuous variables modeled with splines, and clinically relevant pairwise interactions tested if $P<0.001$. Final models were internally validated via bootstrapping to obtain optimism-corrected calibration and discrimination C-indices, and externally validated on a 10% holdout sample from each trial.

Results

All included variables were predictive, with the exception of lung metastases, for overall survival, and total white cell count, derived neutrophil-to-lymphocyte ratio, and sex for progression-free survival. No

clinically relevant pairwise interactions were identified. Nomograms for overall and progression-free survival including remaining variables were well calibrated (C=0.68 and C=0.62, respectively). External validity was good: 72% and 68% concordance, respectively, for 1-year overall and 6-month progression-free survival, between predicted (>50% vs. <50% probability) and actual (yes/no) overall and progression-free survival. Median survival predictions fell within the actual 95% Kaplan-Meier intervals.

Conclusions

The proposed nomograms are well calibrated and internally and externally valid. These tools have the potential to aid prognostication and patient–physician communication and balance risk in colorectal cancer trials

Background and Rationale

Advanced colorectal cancer remains a lethal disease, even though survival from the first diagnosis of metastatic disease has improved significantly over the last 20 years, although substantial heterogeneity in survival outcomes remains. With

improved treatments and understanding of tumor biology, potential prognostic factors have emerged.

Estimating survival is always difficult, even for experienced oncologists; accuracy of estimates is limited even for patients with terminal disease [1], and extrapolating results from clinical trials, where selection bias limits generalisability, is unreliable. The emergence of molecular phenotypes has further complicated prognostication, with limited data to guide clinicians on how these new biomarkers might best be integrated with established prognostic factors and incorporated in new treatment options [2].

Estimating prognosis has several advantages for clinical care. Discussion about prognosis is commonly raised by patients from the time of diagnosis; our inability to accurately predict this has been identified as an important barrier to effective physician-patient communication[3]. While methods exist for estimating and communicating prognosis on the basis of medians [4] derived from clinical trial data, a more precise estimate tailored to individual patient factors is a potentially valuable tool for clinicians.

More accurate prognostication would also be helpful for designing clinical trials to evaluate new treatments. Understanding factors influencing prognosis would allow prognostic groups in randomized trials to be balanced more accurately. This may be particularly useful in smaller trials, where imbalance across arms is more likely, or in historical comparisons for rarer subtypes. Nomograms can also help identify patients suitable for clinical trials where a minimum survival estimate is required, such as the Colon Life application [5], or where a poorer prognosis may warrant treatment escalation.

Large numbers of patients are required to evaluate the relative effects of established and postulated prognostic factors. We were able to access individual patient data from the ARCAD collaborative colorectal cancer database[6], the largest collection of recent randomized phase II and III trials in advanced colorectal cancer. This allowed us to evaluate multiple postulated prognostic factors and their relative contribution, on a scale not possible in individual trials or smaller pooled data sets.

To improve prognostication for clinical practice and trial design, we developed a nomogram to predict progression-free survival (PFS) and overall survival (OS) in patients commencing first-line systemic therapy for advanced or metastatic colorectal cancer from individual patient data in the ARCAD database.

Methods

Database and Candidate Variables

Data from 22,674 patients enrolled to 26 randomized clinical trials for first line treatment of metastatic colorectal cancer were used to construct and independently validate clinical prediction models for PFS and OS. All first-line trials with data included in the ARCAD trial database at June 30, 2016, were eligible. Trial descriptions and contributing sample sizes are shown in Supplementary Table 1. Known prognostic variables were identified, and additional candidates proposed by the ARCAD project team.

Imputation of Missing Data and Construction/Validation Datasets

Potential prognostic variables were examined for individual and joint missingness and considered for imputation. The missing-at-random assumption (that

conditional on observed data, unobserved data are missing at random) was used, as most missingness was study specific (for example, a data item not consistently collected on study case-report forms for all patients in that trial). Given the large dataset, independent variables with at least 35% availability across patients could be imputed. We used stochastic regression imputation and included all available variables (including outcomes and study) in the final imputation model [7, 8]. Independent variables missing data for more than 65% of patients (such as side of the primary tumor) were not considered candidates for imputation and modeling, with the exception of BRAF, which was included for its importance as a molecular prognostic factor [7]. Patient outcome data (PFS and OS) were not imputed, and patients for whom clinical outcomes were not recorded (such as those deemed ineligible within their respective trials) were excluded from analyses.

Following imputation of missing data, the overall ARCAD database was split into a construction dataset of 20,417 patients comprising a random sample of 90% of patients from each clinical trial, and a validation dataset of 2,257 patients comprising the remaining 10% from each trial.

Univariable Models

After imputation and using the construction dataset, we examined the following variables for univariable associations with OS and PFS: age (continuous)[9], sex, body mass index (BMI; continuous)[10], performance status (PS; 0, 1, 2+), prior chemotherapy use for any reason (yes, no), KRAS or BRAF

mutation, number of organs with metastatic involvement (0-1, 2+), presence versus absence of liver, lung[11], peritoneal[12], or nodal metastases, and laboratory markers including white blood cell count (WBC), platelets, hemoglobin, absolute neutrophil count, bilirubin, albumin, neutrophils, and derived neutrophil-to-lymphocyte ratio[13]. For each variable and outcome of interest, univariable Cox proportional-hazards regression models stratified by treatment arm within each study were fit, allowing effects to be averaged across study-specific baseline hazard functions. Continuous variables (age, BMI, and node ratio) were modeled by using restricted cubic splines to test for possible nonlinearity of their effects on the log relative hazard of outcome; where significant nonlinearity was identified, splines were also used in multivariable modeling, and otherwise variables were subsequently modelled as linear on the log relative-hazard scale [8, 14]. The proportional-hazards assumption for each variable was tested using the methods of Grambsch and Therneau [15]. Variables showing both statistical significance at $P < 0.05$ and clinical significance as assessed by hazard ratios were graduated to subsequent interaction testing and multivariable modeling.

Tests for Two-Way Interactions

To determine whether the effects of any covariates were dependent on other covariates, all pairs of variables showing univariable significance were tested for two-way interaction. Statistically significant ($p < 0.01$) interaction and clinically differentiable effect mediation were required for subsequent consideration in final models. Higher-ordered interactions were not examined for reasons of interpretability and reproducibility.

Model Construction

Multivariable Cox proportional-hazards models for OS and PFS were formulated from all variables and two-way interactions demonstrating statistically and clinically significant associations with their respective endpoints, where clinical significance was achieved if the effect of one variable (e.g., hazard ratio) differed in a clinically meaningful way across levels of the other variable in the interaction. After backwards stepwise elimination, final models included all main effects and pairwise interactions remaining statistically ($P < 0.05$) and clinically significant after adjustment. Nomograms (calculators) based on the final models were constructed for the likelihood of PFS at 6 months and OS at 1 year. All statistical tests were two-sided, and all imputation, analyses, and figures were produced using “rms”, part of R statistical software, version 3.2.1 [16].

Internal Validation

Final models for OS and PFS were internally validated using bootstrapping resampling of the construction dataset (with 1,000 bootstrap samples per model) to obtain optimism-corrected discrimination via the concordance index for survival data and calibration plots [8, 14].

External Validation

External validation was performed by comparing the predicted 6-month PFS and 1-year OS probabilities of patients from the 10% validation set and the observed outcomes of the same patients. For each endpoint, the median ARCAD-based prediction across patients was compared with the observed Kaplan-Meier estimate (and its confidence interval) for the same patients and time point, overall and within patient subgroups. As another measure of external validation, rates of correct prediction, that is, the concordance of observed (event, no event) and predicted (using 50% predicted probability as a dichotomizing threshold) 6-month PFS and 1-year OS status across validation set patients and subgroups were also computed.

Results

Descriptive Statistics

The distribution of each variable was maintained with imputation (Table 1). Patients were primarily male (62%) with median age 62 years (interquartile range: 55 to 69 years). More than half (53%) of patients had performance status 0, 69% had colon-only primary tumors, 59% had two or more sites of metastatic disease, and 79% had never received chemotherapy for any reason.

Single Variable Models and Two-Way Interaction Testing

All variables demonstrated some degree of statistical and clinical significance in univariable models for PFS and OS; therefore, all variables were carried forward for potential inclusion in the final multivariable models. However, no statistically significant and clinically relevant interactions were identified for either endpoint,

where clinical relevance was judged via examination of spline plots for continuous variables and hazard ratios for categorical variables across subgroups.

Final Multivariable Models

The final multivariable models for OS and PFS are presented in Table 2, and corresponding nomograms for OS and PFS are presented in Figure 1.

Overall Survival

Patient and disease variables significantly associated with lower survival in multivariable modeling included young or old age ($p < 0.001$), male sex (HR = 1.05; $P = 0.02$), low BMI ($p < 0.001$), and worsened performance status (PS1/PS0 HR = 1.31; PS2+/PS0 HR = 1.73; $P < 0.001$). Prior chemotherapy for any reason was also associated with a 15% increased risk of death (HR = 1.15; $P < 0.001$). KRAS mutant status was associated with a higher likelihood of death during follow-up (HR = 1.35; $P < 0.001$); similarly, BRAF mutant status was associated with a higher risk of death (HR = 2.21; $P < 0.001$). Presence of two or more metastatic sites was associated with higher risk of death than 0 or 1 metastatic sites (HR = 1.20; $P < 0.001$), as was the presence of liver metastases (HR = 1.20; $P < 0.001$), lymph node metastases (HR = 1.15; $P < 0.001$), and peritoneal metastases (HR = 1.19; $P < 0.001$). Among the baseline laboratory markers considered, higher levels of platelets ($p < 0.001$), WBC ($p = 0.02$), and neutrophils ($p < 0.001$) were associated with a higher risk of death, while elevated hemoglobin ($p < 0.001$) and albumin ($p < 0.001$) were associated with lower risk. Primary tumor site (colon versus rectum), presence versus absence of lung metastases, and baseline derived neutrophil-to-lymphocyte ratio (dNLR) were not associated with OS after adjustment for other factors.

Progression-Free Survival

Patient and disease variables significantly associated with lower PFS in multivariable models included young or old age ($p = 0.04$), male sex (HR = 1.03; $P = 0.04$), low BMI ($p < 0.001$), and poorer performance status (PS1/PS0 HR = 1.17; PS2+/PS0 HR = 1.40; $P < 0.001$). Prior chemotherapy was associated with 12% higher risk of disease progression or death ($p < 0.001$) during follow-up. KRAS mutant status was also associated with 30% higher likelihood of progression or death (HR = 1.30; $P < 0.001$); similarly, BRAF mutant status was associated with an 85% higher chance of progression or death (HR = 1.85; $P < 0.001$). Presence of two or more metastatic sites, compared with 0 or 1, was associated with 12% higher risk of progression(HR = 1.12; $P < 0.001$), having lung metastases (HR = 1.11; $P < 0.001$), liver metastases (HR = 1.14; $P < 0.001$), lymph node metastases (HR = 1.08; $P < 0.001$), and peritoneal metastases (1.06; $P = 0.02$) were each significantly associated with higher risk of progression. Among the baseline laboratory markers considered, higher levels of platelets ($p < 0.001$), neutrophils ($p < 0.001$), or bilirubin ($p < 0.001$) were associated with higher risk of progression , while elevated hemoglobin ($p < 0.001$) and albumin ($p < 0.001$) were associated with lower risk. Primary tumor location (colon versus rectum), baseline WBC, and baseline dNLR were not associated with PFS after adjustment for other variables.

While familiarity with nomograms is not required to use the web-based tools, brief instructions are provided in the Appendix. From Figure 1, the relative prognostic importance of each variable for each outcome may be readily gauged; for example,

levels of baseline neutrophils and albumin have the largest impact on OS risk, while sex has the smallest (but still clinically relevant) impact.

Internal Validation

The final model for OS had an adjusted concordance index (C) of 0.68, and the model for PFS yielded C = 0.62. Calibration of observed versus predicted 1-year OS and 6-month PFS was strong across the spectrum of ordered risk groups (Figure 2).

External Validation

External validation results for OS and PFS are shown in Table 3.

Overall Survival

The 1-year survival of the validation set of patients had high concordance: 73%. When median (across patients) 1-year OS predictions obtained from the ARCAD calculator were compared with the observed Kaplan-Meier 1-year OS rates, predictions fell within 5% of the actual rates, both overall and within most of the subgroups defined by those variables appearing in the ARCAD calculators (Table 3), although the calculator trended toward overestimation of survival to a small degree. In most patient subgroups, predictions fell within the 95% confidence intervals of the Kaplan-Meier rates, demonstrating strong agreement.

Progression-Free Survival

Strong external validation results were observed for PFS, with 68% concordance of predicted and observed 6-month PFS status. The median predicted 6-month PFS rates obtained from the ARCAD calculator were within 5% of the corresponding actual rates, overall and within most patient subgroups (Table 3). Predictions fell within the 95% confidence intervals for the actual Kaplan-Meier rates

in most subgroups, again showing strong predictive accuracy for most types of patients.

Discussion

Using the ARCAD database, we were able to develop internally and externally valid nomograms that were accurate for both PFS and OS. They highlight the relative contribution of baseline clinicopathologic variables to survival estimates, using information that is generally available in the clinic at the time of diagnosis of metastatic disease. The large amount of data used to develop these nomograms allowed assessment of a variety of potential prognostic factors and their relative contributions to survival outcomes.

The largest contributions to PFS and OS come from those factors previously established as prognostic in other datasets. Albumin, and other markers of inflammation combined, contributed significantly, along with performance status. While tumor factors, including mutation status (BRAF, KRAS), were included in the final model, a substantial proportion of prognostic information is contributed by patient factors: for example sex, performance status, low BMI[17], and laboratory values. This highlights the importance of considering prognostic biomarkers beyond the immediate tumor environment.

The included clinical trial populations did not represent the full spectrum of patients in the clinic. Although trials of reduced-intensity treatment[18] and more poorly performing populations were included, the generalizability of the nomograms beyond the types of patients included in the database is unknown. Although the models are well calibrated and accurate, they could be updated in future by including additional biomarkers found to be prognostic. Other potentially prognostic variables,

such as blood-based tumor markers at baseline (for example, carcinoembryonic antigen), could not be included, as sufficient data were not collected. Tumor location within the colon (sidedness), in particular, was not included, although tumor site (colon or rectum) was considered, but not significant. While this limitation is acknowledged, and additional analyses including tumor location would be of interest, the overall impact of adding this to the current model is likely to be limited. Although tumor location is prognostic in retrospective analyses of patients with all-RAS wild-type tumors receiving first-line systemic therapies[19], the effect on RAS-mutant tumors has not been examined, and relatively few patients in chemotherapy-alone arms were included. Restricting analyses to only those patients for whom sidedness was known would have substantially reduced the numbers and limited the ability to evaluate a comprehensive list of prognostic factors.

These nomograms were intended to be purely prognostic and, as such, assume treatment has been delivered according to best practice, in a patient cohort eligible for clinical trials. No evaluation of the predictive effect on treatment response was intended. This model cannot therefore estimate outcomes in the absence of systemic therapy, at commencement of later lines of therapy, or with different treatment types. Nor is it intended to be used to evaluate outcomes from different therapies or to select between them. Although an online calculator is planned to make these nomograms more readily available, clinicians need to consider these caveats when counselling patients on likely outcomes of treatment for individual patients.

The ability to more accurately predict individual outcomes is a key factor in personalising therapy for metastatic colorectal carcinoma. The developed nomograms are able to accurately describe outcomes for patients with metastatic

colorectal carcinoma who are about to commence first-line therapy, and are the most comprehensive developed to date. The models highlight key clinical and pathological factors associated with prognosis and their relative contributions.

Conclusions

The proposed nomograms are well calibrated and internally and externally valid. These tools use easily accessible clinicopathologic information in patients with metastatic colorectal carcinoma before commencment of first-line systemic therapy. They have the potential to aid prognostication and patient/physician communication, and balance risk in randomized trials in metastatic colorectal carcinoma. Development of a web-based tool is underway.

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Table 1. Demographics and disease characteristics of patients used for nomogram construction: pre-imputation and post-imputation.

	Pre-Imputation		Post-Imputation	
Characteristic	**No.**	**%**	**No.**	**%**
Age (years)				
Mean (SD)	61 (11)		61 (11)	
Median (IQR)	62 (55, 69)		62 (55, 69)	
(Missing)	(7)	(0)	(0)	(0)
Sex				
Male	13,954	62	13,965	62
Female	8,702	38	8,709	38
(Missing)	(18)	(0)	(0)	(0)
BMI				
Mean (SD)	26 (5)		26 (5)	
Median (IQR)	25 (23, 29)		25 (23, 29)	

(Missing)	(1,525)	(7)	(0)	(0)
PS				
0	11,997	53	12,123	53
1	9,496	42	9,595	42
2+	948	4	956	4
(Missing)	(233)	(1)	(0)	(0)
Location				
Colon	11,826	69	15,691	69
Rectum	5,030	29	6,615	29
Both	283	2	368	2
(Missing)	(5,535)	(24)	(0)	(0)
# Met Sites				
0-1	7,611	43	9,409	41
2+	10,235	57	13,265	59
(Missing)	(4,828)	(21)	(0)	(0)
Liver Mets				
Yes	14,422	78	17,632	78
No	4,088	22	5,042	22
(Missing)	(4,164)	(18)	(0)	(0)
Lung Mets				
Yes	6,647	37	8,559	38
No	11,242	63	14,115	62
(Missing)	(4,785)	(21)	(0)	(0)
LN Mets				
Yes	6,140	39	8,845	39
No	9,643	61	13,829	61
(Missing)	(6,891)	(30)	(0)	(0)
Peritoneal Mets				
Yes	1,624	16	4,261	19
No	8,626	84	18,413	81
(Missing)	(12,424)	(55)	(0)	(0)
Prior Chemo				
Yes	4,331	21	4,779	21
No	16,206	79	17,895	79
(Missing)	(2,137)	(9)	(0)	(0)
KRAS				
Mutant	3,033	38	8,924	39
Wild-Type	4,896	62	13,750	61
(Missing)	(14,745)	(65)	(0)	(0)
BRAF				
Mutant	388	8	1,921	8
Wild-Type	4,421	92	20,753	92
(Missing)	(17,865)	(79)	(0)	(0)
WBC ($x10^9$/L)				
Mean (SD)	8.4 (3.4)		8.5 (3.4)	
Median (IQR)	7.8 (6.3, 9.7)		7.8 (6.4, 9.7)	
(Missing)	(4,442)	(20)	(0)	(0)
Platelets ($x10^9$/L)				

Mean (SD)	335 (128)		334 (127)	
Median (IQR)	310 (245, 398)		309 (245, 398)	
(Missing)	(1,899)	(8)	(0)	(0)
Albumin (g/L)				
Mean (SD)	39 (6)		39 (6)	
Median (IQR)	40 (36, 43)		39 (36, 42)	
(Missing)	(14,695)	(65)	(0)	(0)
Hgb (g/dL)				
Mean (SD)	12.4 (1.7)		12.4 (1.7)	
Median (IQR)	12.4 (11.2, 13.6)		12.4 (11.1, 13.6)	
(Missing)	(7,618)	(34)	(0)	(0)
ANC (x10^9/L)				
Mean (SD)	5.7 (2.7)		5.6 (2.6)	
Median (IQR)	5.1 (3.9, 6.8)		5.2 (4.0, 6.6)	
(Missing)	(6,480)	(29)	(0)	(0)
Bilirubin (mg/dL)				
Mean (SD)	0.63 (0.94)		0.63 (0.92)	
Median (IQR)	0.50 (0.34, 0.69)		0.50 (0.34, 0.69)	
(Missing)	(3,021)	(13)	(0)	(0)
dNLR				
Mean (SD)	2.4 (1.4)		2.5 (2.3)	
Median (IQR)	2.1 (1.5, 2.8)		2.0 (1.4, 2.9)	
(Missing)	(8,516)	(38)	(0)	(0)
TOTAL	**22,674**	**100**	**22,674**	**100**

Abbreviations: No, number; %, percentage; SD, standard deviation; IQR, Interquartile Range; BMI, body mass index; PS, ECOG/WHO performance status; Mets, metastases; LN, lymph node; WBC, white blood cell; Hgb, hemoglobin; ANC, absolute neutrophil count; dNLR, derived neutrophil-to-lymphocyte ratio.

Table 2. Final multivariable Cox models associated with nomogram for OS and PFS. Variables with shaded regions did not significantly contribute to their respective models.

	Overall Survival (OS)				Progression-Free Survival (PFS)			
Variable	**Coef**	**Std Err**	**HR**	**p-Value**	**Coef**	**Std Err**	**HR**	**p-Value**
Age	-0.0012 0.0078	0.0017 0.0020	**	<0.0001	-0.0036 0.0045	0.0015 0.0018	**	0.0384
Sex				0.0177				0.0409
Female	-	-	-		-	-	-	
Male	0.0442	0.0186	1.045		0.0342	0.0167	1.035	
BMI	-0.0236 0.0167	0.0046 0.0055	**	<0.0001	-0.0133 0.0101	0.0042 0.0049	**	0.0006
PS				<0.0001				<0.0001
0	-	-	-		-	-	-	
1	0.2663	0.0184	1.305		0.1599	0.0166	1.173	
2+	0.5471	0.0407	1.728		0.3358	0.0395	1.400	
Prior Chemo				<0.0001				<0.0001
No	-	-	-		-	-	-	
Yes	0.1358	0.0237	1.145		0.1124	0.0211	1.119	
KRAS				<0.0001				<0.0001
Wild-Type	-	-	-		-	-	-	
Mutant	0.3000	0.0181	1.350		0.2623	0.0163	1.300	
BRAF				<0.0001				<0.0001
Wild-Type	-	-	-		-	-	-	
Mutant	0.7922	0.0304	2.208		0.6125	0.0285	1.845	
Platelets ($x10^9$/L)	0.0012 -0.0013	0.0002 0.0003	**	<0.0001	0.0009 -0.0009	0.0002 0.0002	**	<0.0001
WBC ($x10^9$/L)	0.0063	0.0027	1.006	0.0173				
Hgb (g/dL)	-0.0449	0.0063	0.956	<0.0001	-0.0229	0.0056	0.9774	<0.0001
Albumin (g/L)	-0.0481 0.0097	0.0032 0.0036	**	<0.0001	-0.0273 0.0097	0.0031 0.0032	**	<0.0001
ANC ($x10^9$/L)	0.1129 -0.0767	0.0069 0.0118	**	<0.0001	0.0274	0.0033	1.028	<0.0001
Bilirubin	0.4842	0.0758	**	<0.0001	0.2376	0.0679	**	<0.0001

(mg/dL)	-0.5016	0.0831			-0.2332	0.0745		
# Met Sites				<0.0001				<0.0001
0-1	-	-	-		-	-	-	
2+	0.1859	0.0224	1.204		0.1103	0.0247	1.117	
Liver				<0.0001				<0.0001
No	-	-	-		-	-	-	
Yes	0.1811	0.0240	1.198		0.1304	0.0230	1.139	
LN				<0.0001				0.0003
No	-	-	-		-	-	-	
Yes	0.1375	0.0214	1.147		0.0740	0.0206	1.077	
Peritoneal				<0.0001				0.0153
No	-	-	-		-	-	-	
Yes	0.1706	0.0248	1.186		0.0586	0.0242	1.060	
Lung								<0.0001
No					-	-	-	
Yes					0.1029	0.0204	1.108	

-

Abbreviations: Coef, coefficient; Std Err, standard error; HR, hazard ratio; BMI, body mass index; WBC, white blood cells; Hgb, hemoglobin; ANC, absolute neutrophil count; # Met Sites; number of organs with metastatic involvement; LN, lymph node metastases. (-) denotes reference groups for hazard ratio construction.

** Single hazard ratio not available due to nonlinear effect for these continuous variables

Table 3. Results of external validation of the ARCAD nomograms for OS and PFS, with comparison of 6-month PFS and 1-year OS predictions. Validation based on 2,257 patients comprising a 10% holdout sample from each trial. Median predictions in bold text fall inside the observed 95% K-M CI. Absolute values of Delta (difference between observed and expected rates) less than 5% are also bold.

		Overall Survival (OS)				Progression-Free Survival (PFS)			
		Observed 1-Year OS (%)		Predicted 1-Year OS (%)	% Delta: Predicted - Observed	Observed 6-Month PFS (%)		Predicted 6-Month PFS (%)	% Delta: Predicted - Observed
Group	**N**	**K-M**	**95% CI**			**K-M**	**95% CI**		
Overall	2,257	69.8	(67.9, 71.7)	71.9	**2.1**	66.7	(64.8, 68.7)	64.5	**-2.2**
Age									
<70	1,641	72.1	(69.9, 74.3)	**73.2**	**1.1**	67.4	(65.2, 69.8)	65.0	**-2.4**
70+	616	63.6	(59.8, 67.6)	**69.0**	5.4	64.5	(60.7, 68.4)	**63.0**	**-1.5**
Sex									
Male	1,385	70.8	(68.4, 73.3)	**72.5**	**1.7**	68.1	(65.7, 70.7)	65.4	**-2.7**
Female	872	68.1	(65.0, 71.3)	**71.1**	**3.0**	64.2	(61.1, 67.6)	**63.4**	**-0.8**
PS									
0	1,183	77.1	(74.7, 79.6)	**77.0**	**-0.1**	71.5	(69.0, 74.2)	68.2	**-3.3**
1	964	64.2	(61.2, 67.4)	**66.4**	**0.2**	63.0	(60.0, 66.2)	**61.0**	**-2.0**
2+	110	39.3	(31.1, 49.6)	**45.0**	5.7	45.9	(37.4, 56.2)	**49.9**	**4.0**
BMI									
< 25	1,029	65.3	(62.4, 68.3)	69.1	**3.8**	64.6	(61.7, 67.6)	**63.0**	**-1.6**
25+	1,228	73.2	(70.8, 75.8)	**74.0**	**0.8**	68.4	(65.8, 71.1)	**66.1**	**-2.3**
Pr Chemo									
No	1,824	69.5	(67.4, 71.7)	**71.3**	**1.8**	66.5	(64.4, 68.8)	64.2	**-2.3**
Yes	433	70.6	(66.4, 75.1)	75.4	**4.8**	67.6	(63.2, 72.2)	**65.7**	**-1.9**
BRAF									
WT	2,063	71.8	(69.9, 73.8)	**73.2**	**1.4**	68.7	(66.7, 70.8)	65.5	**-3.2**
Mut	194	47.7	(41.0, 55.4)	**52.1**	**4.4**	45.8	(39.2, 53.4)	**49.6**	**3.8**
KRAS									
WT	1,374	71.0	(68.6, 73.5)	74.9	**3.9**	68.6	(66.2, 71.2)	**68.0**	**-0.6**
Mut	883	67.9	(64.8, 71.1)	**68.3**	**0.4**	63.7	(60.5, 67.0)	**61.1**	**-2.6**
Plt ($x10^9$/L)									
< 310	1,132	75.8	(73.3, 78.4)	**76.2**	**0.4**	71.5	(68.9, 74.2)	67.8	**-3.7**

310+	1,125	63.4	(60.6, 66.3)	66.6	**3.2**	61.9	(59.1, 64.8)	**61.4**	**-0.5**
WBC ($x10^9$/L)									
< 8.0	1,199	76.6	(74.2, 79.0)	**76.4**	**-0.2**	71.3	(68.7, 73.9)	67.4	**-3.9**
8.0+	1,058	61.8	(58.9, 64.9)	65.5	**3.7**	61.3	(58.4, 64.4)	**61.1**	**-0.2**
Hgb (g/dL)									
< 12.4	1,132	62.7	(59.9, 65.6)	66.8	6.1	62.1	(59.3, 65.0)	**61.6**	**-0.5**
12.4+	1,125	76.9	(74.4, 79.4)	**75.9**	**-1.0**	71.4	(68.8, 74.1)	67.3	**-4.1**
Alb (g/L)									
< 40.0	1,208	60.8	(58.1, 63.7)	65.7	**4.9**	60.1	(57.4, 63.0)	**60.9**	**0.8**
40.0+	1,049	80.0	(77.6, 82.5)	**77.9**	**-2.1**	74.2	(71.5, 76.9)	68.5	-5.7
ANC ($x10^9$/L)									
< 5.2	1,172	76.3	(73.9, 78.8)	**76.7**	**0.4**	71.2	(68.7, 73.9)	67.5	**-3.7**
5.2+	1,085	62.4	(59.5, 65.4)	65.6	**3.2**	61.6	(58.8, 64.6)	**61.3**	**-0.3**
Bili (mg/dL)									
< 0.50	1,115	71.8	(69.1, 74.5)	**73.3**	**1.5**	67.7	(64.9, 70.5)	**65.2**	**-2.5**
0.50+	1.142	67.8	(65.1, 70.6)	70.8	**3.0**	65.7	(63.0, 68.6)	**63.9**	**-1.8**
# Met Sites									
0-1	965	75.2	(72.5, 78.1)	**76.8**	**1.6**	70.0	(67.1, 73.0)	**69.1**	**-0.9**
2+	1,292	65.6	(63.1, 68.3)	**67.6**	**2.0**	64.2	(61.6, 66.9)	61.5	**-2.7**
Liver									
No	495	72.9	(69.0, 77.0)	**76.2**	**3.3**	68.1	(64.0, 72.3)	**67.4**	**-0.7**
Yes	1,762	68.8	(66.7, 71.1)	**70.6**	**1.8**	66.3	(64.1, 68.6)	63.9	**-2.4**
Lung									
No	1,410	70.2	(67.9, 72.7)	**72.5**	**2.3**	66.3	(63.9, 68.9)	**66.2**	**-0.1**
Yes	847	69.0	(65.9, 72.2)	**70.9**	**1.9**	67.4	(64.3, 70.7)	62.3	-5.1
LN									
No	1,385	71.7	(69.3, 74.1)	**73.9**	**2.2**	68.9	(66.5, 71.4)	**66.2**	**-2.7**
Yes	872	66.6	(63.5, 69.8)	**67.9**	**1.3**	62.9	(59.8, 66.3)	**62.1**	**-0.8**
Peritoneal									
No	1,818	71.1	(69.0, 73.3)	73.4	**2.3**	67.3	(65.2, 69.5)	**65.4**	**-1.9**
Yes	439	64.0	(59.5, 68.8)	**65.8**	**1.8**	64.3	(59.9, 69.0)	**60.9**	**-3.4**

Abbreviations: K-M, Kaplan-Meier; CI, confidence interval;

Figure legends

Figure 1. Nomograms for (A) overall survival and (B) progression-free survival. See Appendix for instructions for use.

Figure 2. Calibration plots for (A) overall survival and (B) progression-free survival nomograms.