A simple prognostic model for overall survival in metastatic renal cell carcinoma

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Abstract

Introduction: The primary purpose of this study was to develop a simpler prognostic model to predict overall survival for patients treated for metastatic renal cell carcinoma (mRCC) by examining variables shown in the literature to be associated with survival.

Methods: We conducted a retrospective analysis of patients treated for mRCC at two Canadian centres. All patients who started first-line treatment were included in the analysis. A multivariate Cox proportional hazards regression model was constructed using a stepwise procedure. Patients were assigned to risk groups depending on how many of the three risk factors from the final multivariate model they had.

Results: There were three risk factors in the final multivariate model: hemoglobin, prior nephrectomy, and time from diagnosis to treatment. Patients in the high-risk group (two or three risk factors) had a median survival of 5.9 months, while those in the intermediate-risk group (one risk factor) had a median survival of 16.2 months, and those in the low-risk group (no risk factors) had a median survival of 50.6 months.

Conclusions: In multivariate analysis, shorter survival times were associated with hemoglobin below the lower limit of normal, absence of prior nephrectomy, and initiation of treatment within one year of diagnosis.

Introduction

Renal cell carcinoma (RCC) is an aggressive disease, recurring in up to 40% of patients who are initially treated for a localized tumour.[1] About one-third of patients with RCC have metastatic disease at diagnosis.[2,3] Advances in our understanding of the biology of RCC and particularly the role of angiogenesis in the progress of the clear cell subtype have led to the development of oral tyrosine kinase inhibitors with activity mostly against vascular endothelial growth factor receptor 2 (VEGF-2). These novel targeted therapies have transformed the management of metastatic RCC (mRCC).[4,5]

More than 80% of patients achieve clinical benefit in the form of objective response to treatment or disease stabilization with tyrosine kinase inhibitors. Additionally, median overall survival with the targeted therapies is now greater than two years, which is more than double the overall survival seen in the interferon-α era.[6]

Prognostic models that can be used to guide clinical trial design, patient counseling, and treatment decisions have been developed.[7] The Memorial Sloan-Kettering Cancer Centre (MSKCC) model was first published in 1999[8] and remains the standard against which subsequent models for advanced RCC have been assessed.[9] The authors of the model identified Karnofsky performance status, serum lactate dehydrogenase, hemoglobin, corrected serum calcium, and prior nephrectomy (later replaced with time from diagnosis to treatment)[10] as pre-treatment factors predictive of survival and used these factors to categorize patients into three different risk groups. The MSKCC model has since been validated in the era of vascular endothelial growth factor (VEGF)-targeted therapies.[11] Another widely used model was developed by the International Metastatic Renal Cell Carcinoma Database Consortium in 2009,[12] and it has also been externally validated.[11] This model, often referred to as the Heng model, includes four of the five prognostic factors from the MSKCC model (hemoglobin, corrected serum calcium, Karnofsky performance status, and time from diagnosis to treatment), along with two additional ones: neutrophil count and platelet count.[12]

A high neutrophil to lymphocyte ratio (NLR), an index of systemic inflammation, has recently been found in multivariate analyses to be an independent factor for both progression-free survival and overall survival.[13-18]

The primary purpose of this study was to develop a simpler prognostic model to predict overall survival for patients who are treated for mRCC by examining variables shown

in the literature[8,12] to be associated with survival, including NLR. Secondary aims were to compare our model with the MSKCC and Heng models and to analyze survival in the subset of patients on first-line sunitinib therapy.

Methods

Patients

Retrospective data were obtained from the medical records of all patients diagnosed with mRCC at two Canadian centres, from July 2007 until December 2011. The inclusion criteria of Heng and colleagues were used.[9]

We recorded basic demographic, survival, and clinical data, including all variables that have been shown in the literature to be important prognostic factors in mRCC. We used an NLR categorization from the literature (≤3 vs. >3).[19] We retrospectively reviewed data from 120 patients, and included the 89 patients who received at least one cycle of active treatment; 31 patients did not receive treatment and were excluded from the analysis. Approval for this study was obtained from the Horizon Health Network Research Ethics Board.

Statistical analysis

All patients who started first-line treatment, mostly with sunitinib, were included in the analysis. The main outcome, overall survival, was defined as time from treatment initiation until death, otherwise censored at last their last followup or contact. The survival distribution and median survival were assessed via Kaplan Meier estimates. Univariate associations between overall survival and baseline demographic and clinical factors were examined. Significance was taken at $p<0.05$. Log-rank tests were used to test the presence of a significant difference between survival among categorical variables and overall survival. For prognostic purposes, during the model-building phase all continuous variables were dichotomized at the upper or lower levels of normal except for age, which was dichotomized at >65 years and ≤65 years.

A multivariate Cox proportional hazards regression model was constructed using a stepwise procedure to identify the most significant variables affecting the disease-free survival. The stepwise algorithm used the Aikake Information Criterion (AIC), a penalized likelihood measure, to choose a final model. When comparing two models, the model with a lower AIC value more closely resembles reality. The proportional hazards assumption of the final model was examined with a global test of proportionality. The test examines correlations between model residuals and log (time).

The internal validity of the final model was examined with a two-step bootstrap procedure. In the first step, 500 samples were drawn with replacement from the observed data. The model building strategy described above was conducted on all 500 bootstrapped data sets. Finally, the frequency with which each predictor variable appeared in the final model from all 500 samples was counted. Variables appearing in >50% of the models were retained. In the next step, an additional 500 bootstrap samples were obtained. With each sample, a Cox proportional hazards model was fit using the retained variables from the first step. Using the results from the 500 estimated models, mean parameter estimates, hazard ratios, and confidence intervals (CIs) were calculated.

A risk group variable was created by summing the number of risk factors each patient had from the final model. The area under the receiver operating characteristic curve (ROC) was used to determine the predictive accuracy of the risk group variable. Additional risk group variables were calculated using prognostic models from the literature.[8,12] The predictive accuracy of the risk group variables from different prognostic models was assessed with the area under the ROC. Kaplan Meier curves for each of the different risk group variable were calculated.

All analyses were conducted using R version 3.0.1.

Results

Patient characteristics, treatment, and survival

Baseline characteristics are provided in Table 1. Eighty-nine patients were treated for mRCC during the study period. First-line treatments included sunitinib, being the most common (n=71, 79.8%), followed by interferon alpha (n=14, 15.7%), pazopanib (n=2, 2.2%), sorafenib (n=1, 1.1%), and temsirolimus (n=1, 1.1%). Mean patient age was 63.1 years (standard deviation [SD] 9.9 years, range 38–88). Thirty-eight out of the 89 patients (42.7%) were metastatic at diagnosis. There were 17 patients who did not undergo nephrectomy. Of these 17 patients, seven were due to comorbidities; the remaining 10 patients did not have nephrectomy for unknown reasons.

At a median followup of 24.6 months (95% CI 19.2, 39.7) for the entire cohort, the median overall survival was 20.9 months (95% CI 14.2–50.6) (Fig. 1). By the end of the study period, 44 patients (49.4%) had died. One-year survival was 63.7% (95% CI 0.54–0.76).

Univariate analysis

Factors that were significantly associated with poor overall survival were age >65 years, absence of prior nephrectomy, non-clear-cell histology, presence of two or more metastatic sites, presence of brain metastases, time interval from diagnosis to treatment of <1 year, and hemoglobin below the lower limit of normal (Table 2).

Table 1. Participant baseline characteristics		
Categorical variables	**n**	**%**
No. of patients	89	
Gender		
Female	26	29.2
Male	63	70.8
Province		
New Brunswick	80	89.9
Nova Scotia	8	9.0
Prince Edward Island	1	1.1
Treatment		
Sunitinib	71	79.8
Other	18	20.2
Nephrectomy		
No	17	19.1
Yes	72	80.9
Histology		
Clear-cell	72	80.9
Non-clear-cell	17	19.1
Radiation therapy		
No	52	61.2
Yes	33	38.8
Number of metastatic sites*		
1	41	46.6
2	35	39.8
3	12	13.6
Site of metastatic disease		
Lung	63	70.8
Node	27	30.3
Liver	12	13.5
Renal bed	14	15.7
Bone	22	24.7
Brain	9	10.1
Continuous variables	**Mean**	**SD**
Age	63.1	9.9
Hemoglobin (g/L)	125.8	20.2
Corrected calcium (mmol/L)	2.6	0.2
Lactate dehydrogenase (U/L)	250.1	284.2
Alkaline phosphatase (U/L)	119.9.	108.3
Neutrophil-to-lymphocyte ratio	5.3	5.5
Absolute neutrophil count	5.80	2.5
Platelets	297.4	169.6
Karnofsky performance status score	90.5	10.1

*Information on number of metastatic sites was missing for one patient. The percentages in the second column for number of metastatic sites were calculated only for the group of patients for whom data on number of metastatic sites were available.

Multivariate modelling and risk stratification in a new prognostic model

There were three risk factors in the final multivariate model (Table 3): hemoglobin, prior nephrectomy, and time from diagnosis to treatment. Hemoglobin below the lower limit of normal, absence of prior nephrectomy, and having treatment begin within one year of diagnosis were all associated with worse survival. Serum lactate dehydrogenase did not improve the fit of the model in multivariate analysis and was, therefore, not included in the final model.

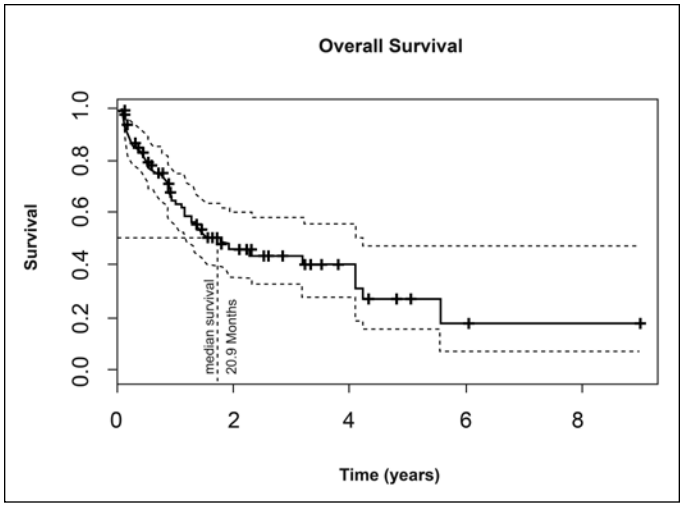

Fig. 1. Overall survival (with 95% confidence limits) of patients in this study. Vertical lines indicate last followup.

Patients were assigned to risk groups depending on how many of these three risk factors they had. Patients with no risk factors were assigned to the favourable-risk group. Patients with one risk factor were assigned to the intermediate-risk group, and patients with two or three risk factors were assigned to the high-risk group. A survival plot based on these risk groups is shown in Fig 2. There were 26 patients (29.2%) in the favourable-risk group, 31 patients (34.8%) in the intermediate-risk group, and 32 patients (36%) in the high-risk group.

Patients in the high-risk group had a median survival of 5.9 months (95% CI 5.9–17.3), while those in the intermediate-risk group had a median survival of 16.2 months (95% CI 11.2–NA), and those in the low-risk group had a median survival of 50.6 months (95% CI 49.3–NA) (Fig. 2).

Comparison between our new model and the MKSCC model

The MKSCC model classifies patients into three risk categories according to their number of risk factors: favourable-risk (no risk factors), intermediate-risk (one or two risk factors), and poor (three, four, or five risk factors). Two of our patients were classified in the favourable group. Grouping these two patients with the intermediate-risk patients would result in 42 of our patients (47.2%) being classified in the intermediate group and 47 (52.8%) in the poor group. There was no difference in survival between the two groups.

Comparison between our new model and the Heng model

The Heng model stratifies patients into three risk categories according to their number of risk factors: favourable-risk (no

Table 2. Univariate analysis of categorical variables and overall survival

Variable	%	% dead	Overall survival (median)	*p* value
Gender				
Male	70.8	44.4	3.2	0.304
Female	29.2	61.5	1.5	
Age				
≤65 years	56.2	46.0	4.11	0.042
>65 years	43.8	53.8	1.18	
Nephrectomy				
No	19.1	76.5	0.35	<0.001
Yes	80.9	43.1	3.19	
Radiation				
No	61.2	48.1	1.92	0.693
Yes	38.8	51.5	1.50	
Treatment				
Sunitinib	79.8	43.7	2.29	0.228
Other	20.2	72.2	1.18	
Histology				
Clear-cell	80.9	48.6	1.92	0.035
Non-clear-cell	19.1	52.9	0.58	
No. of metastatic sites				
1	46.6	43.9	3.19	0.045
≥2	53.4	55.3	1.18	
Metastatic sites				
Lung				
No	28.4	28.0	NA	0.051
Yes	71.6	58.7	1.35	
Node				
No	70.5	51.6	1.90	0.755
Yes	29.5	46.2	1.40	
Liver				
No	86.4	52.6	1.50	0.691
Yes	13.6	33.3	NA	
Renal bed				
No	84.1	50.0	1.50	0.547
Yes	15.9	50.0	4.11	
Bone				
No	75.0	53.0	1.74	0.889
Yes	25.0	40.9	1.35	
Brain				
No	89.8	46.8	2.29	0.003
Yes	10.2	77.8	0.88	
Time to treatment				<0.001
≤1 year	60.5	59.6	0.92	
>1 year	39.5	38.2	4.11	
Hemoglobin				<0.001
<LLN	42.0	67.6	0.75	
≥LLN	58.0	37.3	4.11	
Corrected calcium				0.839
>ULN	12.1	37.5	NA	
≤ULN	87.9	51.7	1.92	
Lactate dehydrogenase				0.361
>ULN	29.3	50.0	1.50	
≤ULN	70.7	48.3	2.29	
Alkaline phosphatase				0.153
>ULN	18.3	53.3	2.29	
≤ULN	81.7	47.7	1.74	
Neutrophil-to-lymphocyte ratio				0.014
>ULN	24.4	61.9	0.46	
≤ULN	75.6	46.2	2.29	
Absolute neutrophil count				0.429
>ULN	14.0	71.4	0.35	
≤ULN	86.0	53.5	1.35	
Platelets				0.483
>ULN	11.8	50.0	NA	
≤ULN	88.2	57.8	1.26	
Karnofsky performance status				0.342
>80	70.3	50.0	1.74	
≤80	29.7	54.5	1.14	

Note: Significant p values are bolded. LLN: lower limit of normal; ULN: upper limit of normal; NA: not applicable.

risk factors), intermediate-risk (one or two risk factors), and high-risk (more than two risk factors).[12]

All 21 patients classified in the favourable-risk category according to the Heng model (Table 4) were also in the favourable-risk group in our model. One of the patients in the intermediate-risk group in our model was classified in the high-risk group of the Heng model. Of the 32 patients classified in our high-risk group, 26 were classified in the Heng model's intermediate-risk group and six were classified in the Heng model's high-risk group.

Fig. 2 also presents a survival plot for patients in our study, using the three risk categories of the Heng model. Twenty-one of our patients (23.6%) were in the favourable-risk group according to the Heng model, 61 (68.5%) were in the intermediate-risk group, and seven patients (7.9%) were in the high-risk group. The log-rank test showed a statistically significant difference between survival curves (chi-square=9.8, degrees of freedom=2, p=0.007). Median survival was 49.3 months for the favourable-risk group, 14.2 months for the intermediate-risk group, and 7.4 months for the high-risk group.

Two of the three risk factors in our model (hemoglobin and time from diagnosis to treatment) were also in the Heng model. Both the Heng model and our model were able to distinguish survival curves between the risk groups they

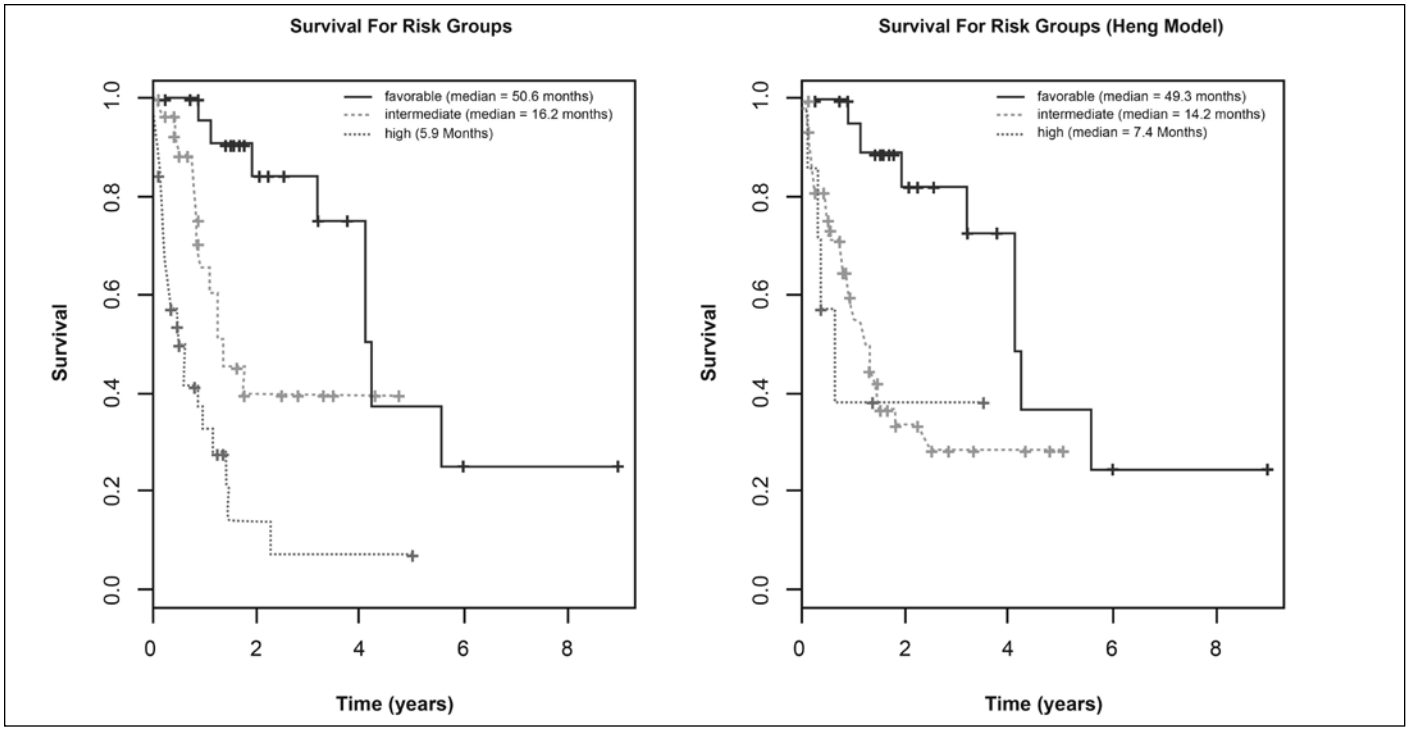

Fig. 2. Side-by-side comparison of survival of patients in our study, stratified according to the three risk groups developed in our model (left) and the Heng model (right). Vertical lines indicate last followup.

produced. Our more parsimonious model was slightly better at predicting survival, as determined by the C-index. The bootstrap corrected C-index was 0.635 for the Heng model and 0.761 for our model.

All 21 patients classified in the favourable-risk category according to the Heng model were also in the favourable-risk group in our model. One of the patients in the intermediate-risk group in the Heng model were classified in the high-risk group of our model and 17 were classified in our favourable-risk group. Five of the patients classified in our high-risk group were classified in the Heng model's intermediate-risk group.

Sub-analysis of patients treated with sunitinib

Of the 89 patients in the study, 71 were treated with sunitinib (Table 1). Overall survival of these patients is shown in Fig. 3. Median survival for this group was 2.29 years. One-year survival was 67.3% (95% CI 56.3–80.5), whereas two-year survival was 53.1% (95% CI 40.7–69.2). Survival up to one year was predicted by the same variables as in our univariate analysis above: NLR, hemoglobin, prior nephrectomy, and time from treatment to diagnosis. This is not surprising, given the proportional hazards assumption. Median followup for patients receiving sunitinib was 21 months (95% CI 18.1–30.4); it was 24.6 months (95% CI 19.2, 39.7) for the entire cohort.

Discussion

In our multivariate analysis, shorter survival times were associated with hemoglobin below the lower limit of normal, absence of prior nephrectomy, and initiation of treatment within one year of diagnosis.

The NLR has been shown elsewhere to be an independent predictor of survival in patients with mRCC[13, 14] and, to our

Table 3. Results of multivariate survival regression and risk group regression

Multivariate Cox proportional hazards regression				Cox proportional hazards regression	
		95% CI			
Predictor	HR	LB	UB	Risk groups	HR
Prior nephrectomy	0.26	(0.14,	0.60)	Intermediate vs. favourable	2.70
Hemoglobin <LLN	0.36	(0.15,	0.52)	High vs. favourable	7.99
Time from diagnosis to treatment <1 year	0.50	(0.23,	1.10)		

CI: confidence interval; HR: hazard ratio; LB, lower bound; LLN: lower limit of normal; UB: upper bound.

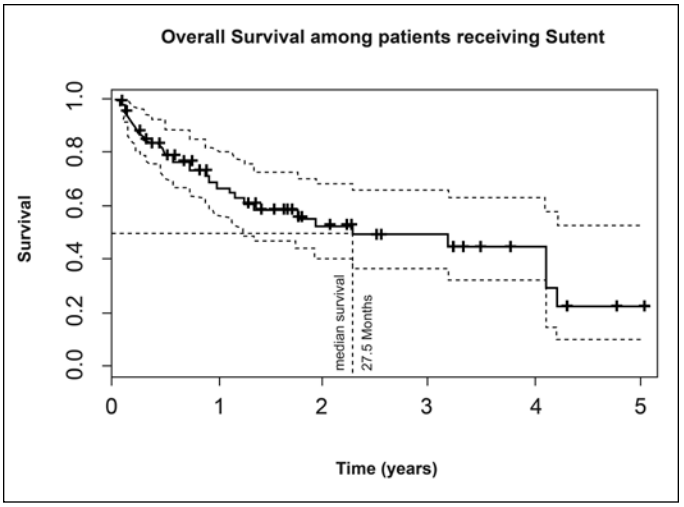

Fig. 3. Survival of the 71 patients (with 95% confidence limits) treated with sunitinib. Vertical lines indicate last followup.

knowledge, it has not yet been considered in any prognostic models. In contrast to recently published articles, our univariate analysis did not demonstrate the independent prognostic value of NLR;[13-18] perhaps this is because only 24% of our study population had an elevated NLR. This finding should be confirmed with a much larger cohort of patients.

Our model was slightly better at predicting survival (C-index 0.761) than the Heng model (0.631). Two of the three risk factors in our model (hemoglobin and time from diagnosis to treatment) were in the Heng model,[12] as well as the 2002 version of the MKSCC model.[10] Our third risk factor, prior nephrectomy, has been shown to be independently associated with overall survival in patients receiving targeted therapy.[20] As Tagawa points out, however, most patients in prospective clinical trials previously underwent nephrectomy, and thus it is difficult to draw conclusions about this factor even though retrospective studies such as ours suggest a benefit.[21] An ongoing prospective clinical trial, the CARMENA trial, is evaluating the value of upfront nephrectomy followed by sunitinib vs. sunitinib alone without nephrectomy in metastatic clear-cell RCC.[22]

Based on multiple prospective phase 3 trials, first-line oral therapy with tyrosine kinase inhibitors directed against VEGF signaling has become the standard of care for most patients with mRCC with clear-cell histology.[4,5] In a population-based study, the introduction of first-line sunitinib was associated with a doubling of overall survival compared with patients treated with interferon alone[23] and it has a manageable safety profile.[24] We were particularly interested in prognostic factors for patients receiving sunitinib. Survival up to one year was predicted by the same variables as in our univariate analysis for the entire study population: hemoglobin, prior nephrectomy, and time from treatment to diagnosis. Barnias etal produced a model for patients treated with sunitinib with three prognostic factors: time from diagnosis to initiation of treatment (as in our analysis), number of metastatic sites, and performance status.[6]

There are limitations to this study, including its retrospective design and the relatively small number of patients included in the analysis. There were missing data for some of the prognostic variables in the patient charts, which may have biased our results.

Our model is simpler and could be validated in a large data bank registry, such as the International Metastatic Renal-Cell Carcinoma Database Consortium or the Canadian Kidney Cancer Information System.

Conclusion

Prognostic models using clinical and laboratory-based variables remain the primary tool for predicting outcomes in mRCC. Our study adds a new set of real-world data to the international efforts to develop better prognostic models.

Competing interests: Dr. Assi has been an Advisory Board member for Pfizer. Dr. Patenaude has received grants/honoraria from BMS, Novartis, Pfizer, and Roche; and has participated in clinical trials for BMS, Merck, Novartis, Pfizer, and Roche. Dr. Toumishey has participated in clinical trials for Celgene. Ms. Ross has participated in numerous clinical trials. Dr. Abdelsalam has been an Advisory Board member for Amgen, Astelllas, BI, Celgene, Eli Lily, Innomar Strategies, Janssen, Johnson & Johnson, Merck, Novartis, and Sanofi; has received grants/honoraria from Amgen, Astellas, BI, Eli Lily, Janssen, Johnson & Johnson, and Roche; and has participated in clinical trials for Amgen, Aragon, Astra Zeneca, BI, BMI, Exelixis, GSK, Merck, Merrimack, NCIC, Novartis, QC Clinical Research Organization in Cancer, Quintiles, Roche, and Serono. Dr. Reiman has received grants/honoraria from Celgene and Roche; and has participated in clinical trials for AstraZeneca, Celgene, Eli Lilly, Genentech, GSK, Takeda, and Roche.

Table 4. Comparison of our model with the Heng model

	Our model			Heng model		
	No. of patients (%)	Median	95% CI	No. of patients (%)	Median	95% CI
Favourable-risk group	26 (29.2)	50.6	49.3–NA	21 (23.6)	49.3	49.3–NA
Intermediate-risk group	31 (34.8)	16.2	11.1–NA	61 (68.5)	14.2	10.5–27.5
High-risk group	32 (36.0)	5.9	3.1–17.3	7 (7.9)	7.4	3.6–NA
Log-rank test	Chi square=30.9, df=2, p<0.001			Chi square=9.8, df=2, p=0.007		
C index	0.761			0.635		

CI: confidence interval; df: degrees of freedom.

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This paper has been peer-reviewed.

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