BRIEF COMMUNICATION

Prognostic Model for Predicting Survival of Patients With Metastatic Urothelial Cancer Treated With Cisplatin-Based Chemotherapy

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A prognostic model that predicts overall survival (OS) for metastatic urothelial cancer (MetUC) patients treated with cisplatin-based chemotherapy was developed, validated, and compared with a commonly used Memorial Sloan-Kettering Cancer Center (MSKCC) risk-score model. Data from 7 protocols that enrolled 308 patients with MetUC were pooled. An external multi-institutional dataset was used to validate the model. The primary measurement of predictive discrimination was Harrell's c-index, computed with 95% confidence interval (CI). The final model included four pretreatment variables to predict OS: visceral metastases, albumin, performance status, and hemoglobin. The Harrell's c-index was 0.67 for the four-variable model and 0.64 for the MSKCC risk-score model, with a prediction improvement for OS (the *U* statistic and its standard deviation were used to calculate the two-sided *P* = .002). In the validation cohort, the c-indices for the four-variable and the MSKCC risk-score models were 0.63 (95% CI = 0.56 to 0.69) and 0.58 (95% CI = 0.52 to 0.65), respectively, with superiority of the four-variable model compared with the MSKCC risk-score model for OS (the *U* statistic and its standard deviation were used to calculate the two-sided *P* = .02).

A widely used model predicting overall survival (OS) for metastatic urothelial cancer (MetUC) patients treated with cisplatin chemotherapy is based on two prognostic factors—visceral (lung, liver, or bone) metastases and Karnofsky performance status less than 80%—was developed at Memorial Sloan-Kettering Cancer Center (MSKCC) (1). In this analysis of 203 patients with MetUC, median OS for patients with zero, one, or two risk factors were 33, 13.4, and 9.3 months, respectively (*P* < .001). This model has been validated in two randomized phase III trials of MetUC patients receiving platinum-based therapy (2,3).

The objective of this study was to develop a pretreatment prognostic model that could be used to predict 1-, 2-, and 5-year survival probability and median OS in MetUC patients treated with cisplatin-based chemotherapy and to improve prognostic accuracy over the MSKCC model.

The development dataset for this study included 308 MetUC patients who received cisplatin-based chemotherapy on seven prospective phase II trials with similar inclusion criteria at MSKCC from 1983 to 2003 (Table 1) (1,4–12). All study participants gave written informed consent for participation in the corresponding clinical trial, and the study protocols were approved by the respective institutional review boards.

The primary endpoint was OS, defined as the time from initiation of chemotherapy until death or date of last follow-up. Predictors of OS were considered based

on the literature (13–20). Univariate and multivariable analyses used the proportional hazards model for predicting OS; proportional hazards assumption was verified using test for weighted residuals (21). The final model was chosen based on univariate and multivariable *P* values (statistically significant if ≤.05). All statistical tests were two-sided. The model was internally validated, and its accuracy was assessed using Harrell's concordance probability, c-index (22). Bootstrap samples (N = 1000) were used to estimate overfitting. The *U* statistic was used to test whether the predictions of the four-variable model in all possible pairs were more concordant with actual observations than the MSKCC risk-score model in the same pairs. Statistical analyses were performed using R (23) and its Design and Hmisc libraries (24).

The MSKCC risk-score and four-variable models were externally validated by an author (S. Halabi) who was not involved in the development of the prognostic model. The validation cohort, CALGB 90102, included 74 MetUC patients treated with cisplatin, gemcitabine, and gefitinib and enrolled from July 2002 to April 2005 with a median follow-up of 72.5 months (Table 1; Supplementary Figure 1B, available online).

In the nomogram development cohort there was no statistically significant difference in OS among the chemotherapy regimens (doxorubicin, gemcitabine, ifosfamide, paclitaxel, and cisplatin (AGITP) median OS = 16.4, 95% confidence interval [CI] = 14.6 to 22.9; ifosfamide, paclitaxel, and cisplatin (ITP) median OS = 18.0, 95% CI = 12.0 to 29.7; methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) median OS = 14.8, 95% CI = 12.1 to 16.7; *P* = .62) (Supplementary Figure 1A, available online). Median survivals by regimen are shown in Table 1. Univariate analyses for predictors of OS included lactate dehydrogenase; albumin, cubic splines using actual values (4 = no additional risk, whereas <4 or >4 = additional risk); hemoglobin, normal vs below normal (below normal for females was <11.5 g/dL and for males was <13 g/dL); Karnofsky performance status, good (≥80)

Table 1. Patient characteristics*

Characteristic	Nomogram development cohort			Validation cohort
	MSKCC MVAC (n = 203)	MSKCC ITP (n = 45)	MSKCC AG-ITP (n = 60)	CALGB 90102 GC-gefitinib (n = 74)
Male:female	163:40	33:12	46:14	58:16
Median age	63	63	62	64
Median KPS, %	80	80	90	90
Visceral disease, %	49	40	33	69
Bone	26	11	10	18
Liver	13	13	10	31
Lung	26	22	18	43
Risk factors, %				
0	33	55	62	30
1	45	41	35	65
2	22	4	3	5
Median survival, months (95% CI)	14.8 (12.1 to 16.7)	18 (12.0 to 29.7)	16.4 (14.6 to 22.9)	12.7
Failed/censored, No.	184/19	37/8	53/7	68/6

*AG-ITP = doxorubicin plus gemcitabine followed by ifosfamide, paclitaxel, and cisplatin; CI = confidence interval; GC = gemcitabine and cisplatin; ITP = ifosfamide, paclitaxel, and cisplatin; KPS = Karnofsky performance status; MSKCC = Memorial Sloan-Kettering Cancer Center; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin.

vs poor (<80); body surface area; alkaline phosphatase; sex; body mass index; and visceral metastases (ie, lung, liver, bone, or other non–lymph node metastasis) present vs absent on standard imaging. All variables except body surface area, sex, and body mass index were statistically significantly associated with OS. Alkaline phosphatase and lactate dehydrogenase were no longer statistically significant after all other predictors were added and were not included in the multivariable model (Supplementary Table 1, available online).

The final multivariable model included visceral metastases ($P < .001$), albumin ($P < .001$), Karnofsky performance status ($P < .001$), and hemoglobin ($P = .005$). The nomogram based on the corresponding proportional hazards model may be used to predict 1-, 2-, and 5-year survival probabilities and median OS (Figure 1).

The model was internally validated with c-index equal to 0.67 (bootstrap corrected c-index = 0.67). Calibration curves for 1-, 2-, and 5-year probability of survival are shown in Supplementary Figure 2 (available online). The differences between predicted and observed median survival in quartiles of patients defined by predicted median OS are 1.5, 0.5, –9.3, and 5.7 months, respectively. To compare the model with the previously developed MSKCC risk-score model (1), another Cox regression model was fitted using only

the risk variable that takes values 0, 1, and 2 based on Karnofsky performance status (>80) and presence of visceral metastasis. This reduced model had a c-index equal to 0.64 (bootstrap corrected = 0.64), which was inferior to the proposed four-variable model ($P = .002$).

When the nomogram was applied to the validation cohort, the c-indices for the four-variable and MSKCC risk-score models were 0.63 (95% CI = 0.56 to 0.69) and 0.58 (95% CI = 0.52 to 0.65), respectively. Superiority of the four-variable model compared with the MSKCC risk-score model remained ($P = .02$).

This study reports and validates a prognostic model for predicting survival probabilities at 1-, 2-, and 5-year survival and median OS in patients with MetUC patients treated with first-line cisplatin-based chemotherapy. This four-variable prognostic nomogram was superior to the MSKCC risk-score model.

The prognosis is quite variable for MetUC patients treated with first-line chemotherapy (2,4–10,25–28), and both patients and clinicians would benefit from knowing the probability of survival.

Prognostic factors and risk-groups are often used in the design, conduction, and analysis of trials in genitourinary malignancies (29). The distribution of prognostic factors within a trial may influence response and survival and bias the

estimated treatment benefit. Pretreatment stratification with this four-variable prognostic model in prospective phase II or III trials in MetUC patients could ensure similarity of cohorts for comparison and reduce the likelihood that survival differences are a function of patient characteristics. The prognostic model may also be used for comparing OS results across phase II trials.

There are multiple strengths of the four-variable model compared with the MSKCC risk-score model beyond statistical superiority. This model incorporates a larger number of MetUC patients from seven protocols. The model was also validated externally using a cooperative group trial.

There are limitations to the four-variable model. First, the patients participated in clinical trials, and there is the potential that the model may not be predictive for patients ineligible for protocol therapy. Moreover, it has yet to be validated in non–cisplatin-treated patients. Second, the model did not include factors such as histology or molecular markers that may influence survival (30–37). Lastly, the 5-year survival in patients with MetUC is less than 10%; therefore, the robustness of the model's 5-year survival prediction is low. Despite these limitations, the model can be used clinically, and this methodology lends itself well for refinement as other prognostic factors are identified in the future.
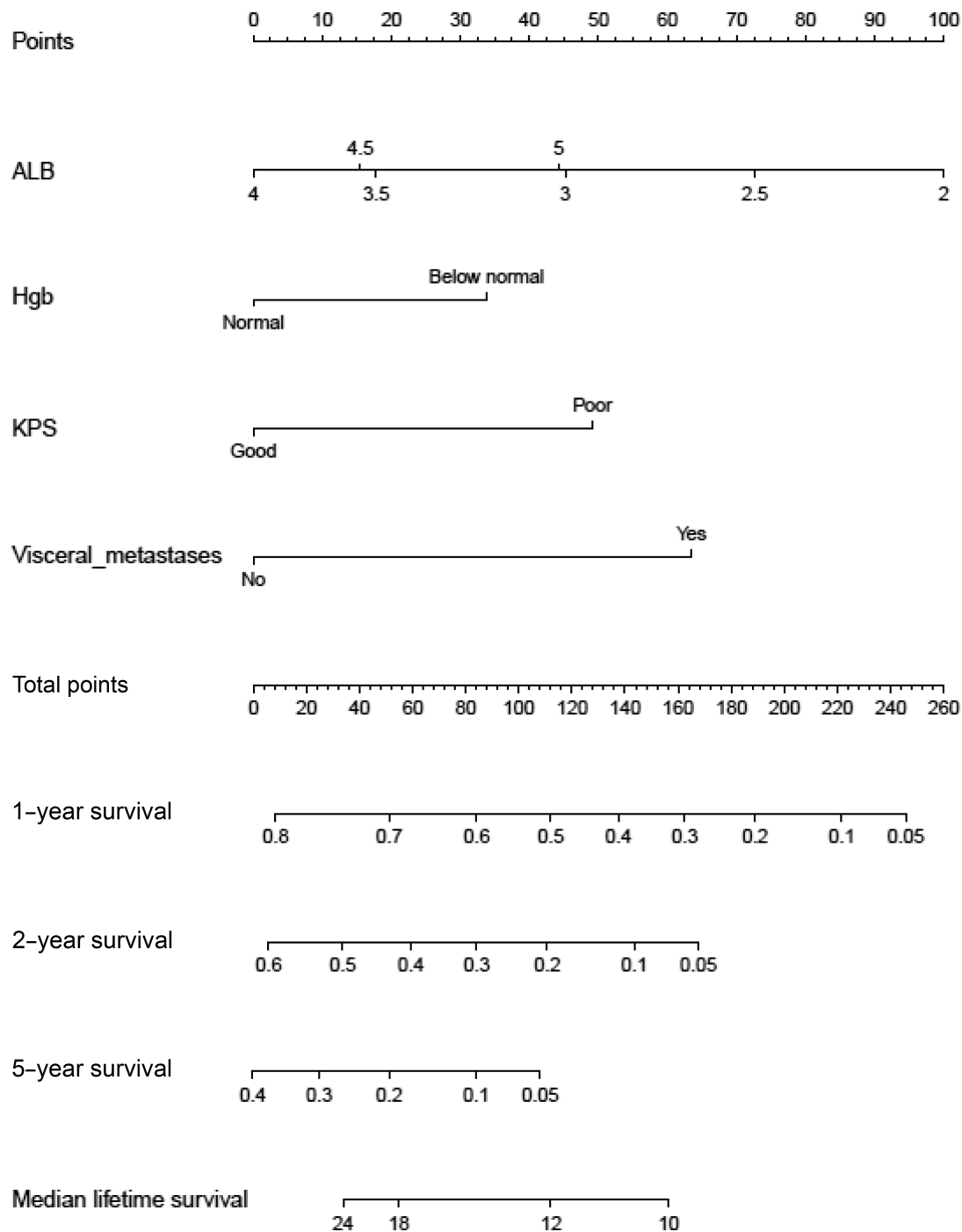
Figure 1. Nomogram for predicting survival of patients with metastatic or unresectable urothelial cancer treated with cisplatin chemotherapy. To estimate survival, calculate points for each predictor by drawing a straight line from patient's value to the axis labeled "Points." Add all points, and draw a straight line from the total point axis to the 1-year, 2-year, 5-year, or median survival (months) axis. ALB = albumin; Hgb = hemoglobin; KPS = Karnofsky performance status.

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