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Kidney Cancer

Development of Accurate Models for Individualized Prediction of Survival After Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma

Vitaly Margulis[a], *Shahrokh F. Shariat*[b], *Yury Rapoport*[a], *Michael Rink*[b], *Daniel D. Sjoberg*[c], *Nizar M. Tannir*[d], *E. Jason Abel*[e], *Stephen H. Culp*[e], *Pheroze Tamboli*[f], *Christopher G. Wood*[e,*]

[a] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA;* [b] *Department of Urology, Weill Cornell Medical Center, New York, NY, USA;* [c] *Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA;* [d] *Department of Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [e] *Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [f] *Department of Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, USA*

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Abstract

Background: There is limited evidence to guide patient selection for cytoreductive nephrectomy (CN) following the diagnosis of metastatic renal cell carcinoma (mRCC).
Objective: Given the significant variability in oncologic outcomes following surgery, we sought to develop clinically relevant, individualized, multivariable models for the prediction of cancer-specific survival at 6 and 12 mo after CN. The development of this nomogram will better help clinicians select patients for cytoreductive surgery.
Design, setting, and participants: We identified 601 consecutive patients who underwent CN for kidney cancer at a single tertiary cancer center.
Intervention: CN for mRCC.
Outcome measurements and statistical analysis: The development cohort was used to select predictive variables from a large group of candidate predictors. The discrimination, calibration, and decision curves were corrected for overfit using 10-fold crossvalidation that included stepwise variable selection.
Results and limitations: With a median follow-up of 65 mo (range: 6–199) for the entire cohort, 110 and 215 patients died from kidney cancer at 6 and 12 mo after surgery, respectively. For the preoperative model, serum albumin and serum lactate dehydrogenase were included. Final pathologic primary tumor stage, nodal stage, and receipt of blood transfusion were added to the previously mentioned parameters for the postoperative model. Preoperative and postoperative nomograms demonstrated good discrimination of 0.76 and 0.74, respectively, when applied to the validation data set. Both models demonstrated excellent calibration and a good net benefit over large ranges of threshold probabilities. The retrospective study design is the major limitation of this study.
Conclusions: We have developed models for accurate prediction of cancer-specific survival after CN, using either preoperative or postoperative variables. While these tools need validation in independent cohorts, our results suggest that the models are informative and can be used to aid in clinical decision making.

* Corresponding author. Department of Urology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA. Tel. +1 713 563 7463; Fax: +1 713 794 4824.
E-mail address: cgwood@mdanderson.org (C.G. Wood).

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1. Introduction

Renal cell carcinoma (RCC) is a common malignancy, representing just >3% of adult solid malignant tumors [1]. While the majority of RCC patients are diagnosed with early-stage, organ-confined disease, approximately 25% of RCC patients demonstrate evidence of systemic metastases at the initial diagnosis [2,3]. Although two randomized controlled trials have demonstrated improved overall survival for patients who undergo cytoreductive nephrectomy (CN) before systemic immunotherapy with interferon-α compared with patients treated with immunotherapy alone, the natural history of metastatic RCC (mRCC) is variable, with median overall survival of just 2 yr [4–6]. The unprecedented antitumor activity and relatively favorable toxicity profile of the modern targeted therapies demand careful reevaluation of the necessity, patient selection, and timing of CN [7–9]. While it is clear that major surgery is inappropriate for someone who has a short life expectancy because of an aggressive cancer, and the decision to give adjuvant therapy is similarly informed by the clinician's estimate of the patient's predicted survival, clinicians are notoriously inaccurate at estimating life expectancy [10,11]. Given the numerous clinical factors shown to be associated with survival in mRCC, we believe that combining these predictors in a multivariable model could help inform decisions about surgery and systemic therapy in patients with mRCC. Such individualized predictive tools, within a context of predicted cancer-specific survival leveraged against potential surgical morbidity, may aid patients and their physicians in the difficult decision-making process related to pursuing a surgical intervention or postsurgical adjuvant therapy.

2. Patients and methods

With approval from the Institutional Review Board for the Protection of Human Subjects at the MD Anderson Cancer Center, the institutional cancer database was queried for patients with mRCC who underwent CN between 1991 and 2008, yielding a cohort of 601 patients. Cancer-specific survival times were calculated from diagnosis to either death or the last known follow-up. Clinical, preoperative laboratory, and final pathologic data variables were collected and re-reviewed to ensure accuracy. Laboratory values immediately prior to CN were used for statistical modeling. Pathologic factors evaluated include histologic classification, presence of sarcomatoid dedifferentiation, Fuhrman nuclear grade, and pathologic staging based on the American Joint Committee on Cancer 2002 TNM classification. The number and sites of metastasis and lymph node involvement were determined based on radiologic imaging.

The primary aim of the study was development of two models to predict death from kidney cancer after CN, based on widely available presurgical and postsurgical variables. Logistic regression analyses rather than survival regression analyses were used because of the availability of sufficient follow-up after CN to have a binary outcome for the early survival times of interest. There were 27 patients excluded from postoperative model development because of lack of sufficient follow-up. To systematically select candidate variables for incorporation into the final model, a forward variable selection process was used based on discrimination.

We began by examining all univariate models. The variable that exhibited the best discrimination was retained. Next, all two-variable models that included the first variable selected were examined. The variable with the best marginal improvement in discrimination was retained. This process was continued until no remaining variables increased the area under the curve by >1%. Variables considered in the preoperative model were number of metastatic organ sites; Eastern Cooperative Oncology Group performance status; time from diagnosis to surgery; preoperative glomerular filtration rate (calculated using the Modification of Diet in Renal Disease formula); serum levels of alkaline phosphatase, lactate dehydrogenase (LDH), corrected calcium, albumin, total and fractionated white blood cells, hemoglobin, platelets, and hematocrit; and Motzer criteria [12]. The postoperative model included the preoperative variables, as well as pathologic TN stage, lymph node density, lymphovascular invasion, tumor grade, operating room time, concomitant retroperitoneal lymphadenectomy, and receipt of a blood transfusion during surgery. The discrimination, calibration, and decision

Table 1 – Clinical and pathologic characteristics of 601 metastatic renal cell carcinoma patients used for model development and validation

Characteristic	Value
Age, yr, median (IQR)	57 (50–64)
Male, no. (%)	417 (69)
BMI, median (IQR)	28 (24–30)
Site of metastases, no. (%)	
Adrenal glands	86 (14)
Bones	174 (29)
Brain	20 (3)
Liver	41 (7)
Lung	410 (68)
Lymph nodes	138 (23)
Other	36 (6)
Metastasis sites, no. (%)	
1	363 (60)
2	175 (29)
3	59 (10)
4	3 (0)
5	1 (0)
LVI, no. (%)	146 (24)
Received blood transfusion, no. (%)	289 (48)
ECOG, no. (%)	
0	405 (67)
1	180 (30)
2	16 (3)
Motzer criteria, no. (%)	
0	145 (24)
1	343 (57)
2	104 (17)
3	8 (1)
4	1 (0)
Pathologic T stage categorized, no. (%)	
T1	71 (12)
T2	70 (12)
≥T3	460 (77)
Tumor grade, no. (%)	
1	2 (0.3)
2	59 (9.8)
3	210 (34.9)
4	330 (54.9)
Albumin, g/dl, median (IQR)	3.90 (3.50–4.20)
Alkaline phosphatase, IU/l, median (IQR)	102 (83–131)
Corrected calcium, mg/dl, median (IQR)	9.3 (9.0–9.7)
Hemoglobin, g/dl, median (IQR)	11.9 (10.5–13.5)
Lactate dehydrogenase, IU/l, median (IQR)	460 (392–586)
Lymphocytes, no. × 10^6/μl, median (IQR)	1.47 (1.08–2.00)
Neutrophils, no. × 10^6/μl, median (IQR)	5.49 (4.20–6.97)
Platelets, no. × 10^6/μl, median (IQR)	316 (242–411)

IQR = interquartile range; BMI = body mass index; LVI = lymphovascular invasion; ECOG = Eastern Cooperative Oncology Group.