Published in final edited form as:

Eur Urol. 2013 May ; 63(5): 947–952. doi:10.1016/j.eururo.2012.11.040.

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

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

^aDepartment of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA

^bDepartment of Urology, Weill Cornell Medical Center, New York, NY, USA

^cDepartment of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

^dDepartment of Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

^eDepartment of Urology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

^fDepartment of Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

Background—There is limited evidence to guide patient selection for cytoreductive nephrectomy (CN) following the diagnosis of metastatic renal cell carcinoma (mRCC).

© 2012 Published by Elsevier B.V. on behalf of European Association of Urology.

*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. cgwood@mdanderson.org (C.G. Wood).

Author contributions: Christopher G. Wood had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Margulis, Wood, Tamboli, Culp.

Acquisition of data: Margulis, Culp, Rapoport, Abel.

Analysis and interpretation of data: Margulis, Shariat, Rink, Sjoberg, Tannir, Abel, Culp, Tamboli, Wood.

Drafting of the manuscript: Margulis, Wood, Shariat.

Critical revision of the manuscript for important intellectual content: Margulis, Shariat, Rapoport, Rink, Sjoberg, Tannir, Abel, Culp, Tamboli, Wood.

Statistical analysis: None.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Margulis, Wood.

Other (specify): None.

Financial disclosures: Christopher G. Wood certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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.

Keywords

Renal cell carcinoma; Cytoreductive nephrectomy; Oncologic outcome; Prediction models

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 curves were corrected for overfit using 10-fold crossvalidation that included the stepwise variable selection.

To determine the clinical value of the model, we used decision curve analysis. This method evaluates the clinical consequences of model predictions by comparing net benefit, based on true positive and false positive, at various threshold probabilities [13]. Decision curve analysis can also be used to estimate the number of surgeries that can be avoided [14]. For example, a patient with a threshold probability of 20% would choose CN if the probability of survival at 6 mo after surgery were 20% and would forgo surgery if the predicted survival were <20%. Since it is unlikely that patients or their physicians would be willing to opt for CN if the predicted survival at 6 or 12 mo were <20% or would chose to forgo CN if the probability of survival were >80%, we examined the range of probability thresholds from 20% to 80% on the decision curve. Statistical analyses were conducted using Stata 11.0 (StataCorp, College Station, TX, USA) and R 2.12.0 supplemented with the design package.

3. Results

Patient characteristics are listed in Table 1. At 6 and 12 mo after surgery, 110 and 215 patients died from kidney cancer, respectively. Median overall survival for the whole cohort was 18 mo. Presurgical and postsurgical systemic therapy was administered in 110 patients (18%) and 471 patients (78%), respectively. Patients treated with presurgical systemic therapy made up a clinical study group in which various systemic agents were evaluated for safety in the presurgical setting and for their effect on molecular end points afforded by treated tissue. None of these patients had a complete response to presurgical therapy in the primary or metastatic sites. The preoperative and postoperative models are presented in Table 2 and 3 and Figure 1. For the preoperative model, serum albumin and serum LDH were included in the predictive model, while the postoperative model included those variables plus pathologic T stage, N stage, and receipt of a blood transfusion during surgery. The relationship between the risk of death and LDH was first investigated univariately using locally weighted regression methods. The knots at 400 and 900 were chosen because they allowed the fitted curve from the logistic regression to follow closely the estimated risk of the LOWESS curve, thus correctly modeling the nonlinear relationship between risk of death and LDH.

Preoperative and postoperative models exhibited good discrimination of 0.76 and 0.74, respectively, when applied to the validation data set. Both models exhibited good calibration, which is expected when using training and validation methods of model development (Fig. 2). Decision curve analysis, shown in Figure 3, demonstrates that the models perform well across a wide range of threshold probabilities. Specifically, both the preoperative and following operative models demonstrated a greater net benefit compared with scenarios in which CN (preoperative model) or adjuvant therapy (postoperative model) is used in all or none of the patients, when examined within the threshold survival probabilities of 20–80%.

4. Discussion

The use of CN in the cytokine therapy era was supported by two randomized trials conducted by the Southwest Oncology Group and by the European Organization for

Research and Treatment of Cancer [4–6]. As we await similar prospective evidence in the context of molecular targeted therapy, mounting retrospective data suggest that appropriately selected patients with mRCC benefit from integration of CN with systemic targeted therapy [9,15]. It is well documented, however, that patients with mRCC display significant variability in oncologic outcomes after CN and systemic therapy [7,16,17]. Thus, validated, accurate, and clinically useful models to predict survival are of paramount importance in the selection of patients for CN, as is avoidance of potentially morbid surgical resection in patients who are unlikely to derive clinical benefit from a surgical intervention. In this paper we have developed and internally validated simple, yet accurate models for prediction of survival at 6 and 12 mo after CN. These models use clinical parameters that are readily available before or after surgery to assign individual prediction of survival after cytoreductive surgery for mRCC. We used a comprehensive data set of clinical and pathologic variables to devise statistically robust models, while making no historical assumptions regarding variable selection and incorporation into the final model. Both models demonstrated good discrimination and calibration. Perhaps more important, both models demonstrated a net benefit across clinically relevant threshold probabilities of survival after CN.

While others have previously shown the association of serum albumin, LDH, and pathologic TN status with oncologic outcomes of mRCC patients, to our knowledge, our study is the first to develop multivariable predictive models of survival in patients deemed appropriate surgical candidates for CN [16,18–24]. Culp et al previously devised a risk group–based model using seven clinical variables available prior to CN [25]. Patients who had four or more adverse parameters did not appear to benefit from surgery, because their overall survival was similar to the cohort of patients with mRCC who received medical therapy alone. In addition to limitations associated with risk-grouping methodologies and lack of internal or external validation, no data regarding calibration, discrimination, or clinical utility were provided [25]. Several other multivariable predictive models have been developed and validated for estimation of oncologic outcomes in all mRCC patients, but to our knowledge, none of the models specifically addresses the surgical cohort that underwent CN [16,22,26,27].

The current study is limited by single-institution experience and lack of external validation. Significant selection bias to undergo surgery may have existed, since CN was aggressively pursued in patients with mRCC at our center; consequently, these findings may not be applicable elsewhere. Patients in this study were treated with a variety of systemic therapies after CN, and the impact of the type and sequencing of such postsurgical treatments could not be evaluated. However, available evidence from cytokine and the targeted therapy eras suggests that CN may provide oncologic benefits independent of the effects of the systemic therapy administered [6,28]. Stated differently, the performance of CN, while providing a perceived survival benefit, was not correlated with response to systemic therapy.

5. Conclusions

The simple and accurate multivariable predictive models described in this exploratory study may aid identification of patients with mRCC who will or will not benefit from CN. If

externally validated, such tools may be of value for treatment decision making, patient counseling, and clinical trial design.

Acknowledgments

Funding/Support and role of the sponsor: None.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011; 61:69–90. [PubMed: 21296855]
2. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Five-year survival after surgical treatment for kidney cancer: a population-based competing risk analysis. *Cancer.* 2007; 109:1763–8. [PubMed: 17351954]
3. Chow WH, Devesa SS. Contemporary epidemiology of renal cell cancer. *Cancer J.* 2008; 14:288–301. [PubMed: 18836333]
4. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet.* 2001; 358:966–70. [PubMed: 11583750]
5. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med.* 2001; 345:1655–9. [PubMed: 11759643]
6. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol.* 2004; 171:1071–6. [PubMed: 14767273]
7. Halbert RJ, Figlin RA, Atkins MB, et al. Treatment of patients with metastatic renal cell cancer: a RAND appropriateness panel. *Cancer.* 2006; 107:2375–83. [PubMed: 17048248]
8. Margulis V, Wood CG. Pre-surgical targeted molecular therapy in renal cell carcinoma. *BJU Int.* 2009; 103:150–3. [PubMed: 19007359]
9. Margulis V, Wood CG, Jonasch E, Matin SF. Current status of debulking nephrectomy in the era of tyrosine kinase inhibitors. *Curr Oncol Rep.* 2008; 10:253–8. [PubMed: 18765156]
10. Ross PL, Gerigk C, Gonen M, et al. Comparisons of nomograms and urologists' predictions in prostate cancer. *Semin Urol Oncol.* 2002; 20:82–8. [PubMed: 12012293]
11. Specht MC, Kattan MW, Gonen M, Fey J, Van Zee KJ. Predicting nonsentinel node status after positive sentinel lymph biopsy for breast cancer: clinicians versus nomogram. *Ann Surg Oncol.* 2005; 12:654–9. [PubMed: 16021535]
12. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol.* 1999; 17:2530–40. [PubMed: 10561319]
13. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making.* 2006; 26:565–74. [PubMed: 17099194]
14. Vickers AJ. Decision analysis for the evaluation of diagnostic tests, prediction models and molecular markers. *Am Stat.* 2008; 62:314–20. [PubMed: 19132141]
15. Crispen PL, Blute ML. Role of cytoreductive nephrectomy in the era of targeted therapy for renal cell carcinoma. *Curr Urol Rep.* 2012; 13:38–46. [PubMed: 22105577]
16. Motzer RJ, Bukowski RM, Figlin RA, et al. Prognostic nomogram for sunitinib in patients with metastatic renal cell carcinoma. *Cancer.* 2008; 113:1552–8. [PubMed: 18720362]
17. Choueiri TK, Rini B, Garcia JA, et al. Prognostic factors associated with long-term survival in previously untreated metastatic renal cell carcinoma. *Ann Oncol.* 2007; 18:249–55. [PubMed: 17060490]
18. Han KR, Pantuck AJ, Bui MH, et al. Number of metastatic sites rather than location dictates overall survival of patients with node-negative metastatic renal cell carcinoma. *Urology.* 2003; 61:314–9. [PubMed: 12597937]

19. Negrier S, Gomez F, Douillard JY, et al. Prognostic factors of response or failure of treatment in patients with metastatic renal carcinomas treated by cytokines: a report from the Groupe Francais d'Immunotherapie. *World J Urol.* 2005; 23:161–5. [PubMed: 15711829]
20. Choueiri TK, Garcia JA, Elson P, et al. Clinical factors associated with outcome in patients with metastatic clear-cell renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *Cancer.* 2007; 110:543–50. [PubMed: 17577222]
21. Pierorazio PM, McKiernan JM, McCann TR, Mohile S, Petrylak D, Benson MC. Outcome after cytoreductive nephrectomy for metastatic renal cell carcinoma is predicted by fractional percentage of tumour volume removed. *BJU Int.* 2007; 100:755–9. [PubMed: 17822456]
22. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol.* 2009; 27:5794–9. [PubMed: 19826129]
23. Ramsey S, Lamb GW, Aitchison M, Graham J, McMillan DC. Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. *Cancer.* 2007; 109:205–12. [PubMed: 17149754]
24. Vasselli JR, Yang JC, Linehan WM, White DE, Rosenberg SA, Walther MM. Lack of retroperitoneal lymphadenopathy predicts survival of patients with metastatic renal cell carcinoma. *J Urol.* 2001; 166:68–72. [PubMed: 11435825]
25. Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? *Cancer.* 2010; 116:3378–88. [PubMed: 20564061]
26. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2004; 22:454–63. [PubMed: 14752067]
27. Karakiewicz PI, Sun M, Bellmunt J, Sneller V, Escudier B. Prediction of progression-free survival rates after bevacizumab plus interferon versus interferon alone in patients with metastatic renal cell carcinoma: comparison of a nomogram to the Motzer criteria. *Eur Urol.* 2011; 60:48–56. [PubMed: 21190790]
28. Choueiri TK, Xie W, Kollmannsberger C, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. *J Urol.* 2011; 185:60–6. [PubMed: 21074201]

Take-home message

Because of significant variability in oncologic outcomes following cytoreductive nephrectomy for renal cell carcinoma, the role of surgery remains controversial. To aid clinical decision making, we have developed and validated multivariable models for the prediction of cancer-specific survival at 6 mo and 12 mo after cytoreductive surgery.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

1A

1B

Fig. 1. (a) Preoperative nomogram and (b) postoperative nomogram for prediction of cancer-specific survival at 6 mo and 12 mo after cytoreductive nephrectomy. LDH = lactate dehydrogenase; KC = kidney cancer

Fig. 2.

(a) Preoperative nomogram calibration plot; (b) postoperative nomogram calibration plot.

The x-axis shows the predicted probability of death according to the nomogram, and the y-axis shows the actual proportion observed in the cohort. Perfect calibration would fall on the black diagonal line, on which predicted risks equal observed rates of death.

Fig. 3.

(a) Preoperative decision curve analysis plot; (b) postoperative decision curve analysis plot.

The dashed line represents the net benefit of the nomogram, the solid gray line represents the treat-all strategy, and the solid black line represents the treat-none strategy.

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)

Characteristic	Value
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. $\times 10^6/\mu\text{l}$, median (IQR)	1.47 (1.08–2.00)
Neutrophils, no. $\times 10^6/\mu\text{l}$, median (IQR)	5.49 (4.20–6.97)
Platelets, no. $\times 10^6/\mu\text{l}$, median (IQR)	316 (242–411)

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

Table 2
Preoperative logistic regression models to predict death from metastatic renal cell carcinoma

Death from kidney cancer within 6 mo			
	OR	95% CI	<i>p</i> value
LDH	NA *	NA *	0.002
Albumin, g/dl	0.207	0.132–0.323	<0.0005

OR = odds ratio; CI = confidence interval; LDH = lactate dehydrogenase; NA = not applicable.

* Modeled with nonlinear terms.

Table 3
Postoperative logistic regression models to predict death from metastatic renal cell carcinoma

	Death from kidney cancer within 12 mo		
	OR	95% CI	<i>p</i> value
N stage			
N0/Nx	Ref.	Ref.	Ref.
N1	1.62	0.746–3.53	0.2
N2	2.97	1.85–4.77	<0.0005
Blood transfusion	2.05	1.37–3.06	<0.0005
T stage T3	2.46	1.43–4.21	0.001
Albumin, g/dl	0.335	0.225–0.500	<0.0005
LDH	NA *	NA *	0.001

OR = odds ratio; CI = confidence interval; Ref. = reference; LDH = lactate dehydrogenase; NA = not applicable.

* Modeled with nonlinear terms.