Published in final edited form as:

Lancet Oncol. 2012 September ; 13(9): . doi:10.1016/S1470-2045(12)70285-1.

Conditional survival of patients with metastatic renal-cell carcinoma treated with VEGF-targeted therapy: a population-based study

Lauren C Harshman, Wanling Xie, Georg A Bjarnason, Jennifer J Knox, Mary MacKenzie, Lori Wood, Sandy Srinivas, Ulka N Vaishampayan, Min-Han Tan, Sun-Young Rha, Frede Donskov, Neeraj Agarwal, Christian Kollmannsberger, Scott North, Brian I Rini, Daniel Y C Heng*, and Toni K Choueiri*

Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA (L C Harshman MD, S Srinivas MD); Dana-Farber Cancer Institute, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA (W Xie MS, T K Choueiri MD); Sunnybrook Odette Cancer Centre, Toronto, ON, Canada (G A Bjarnason MD); Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada (J J Knox MD); London Health Sciences Center, London, ON, Canada (M MacKenzie MD); Queen Elizabeth II Health Sciences Center, Halifax, NS, Canada (L Wood MD); Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA (U N Vaishampayan MD); Department of Medical Oncology, National Cancer Centre and Institute of Bioengineering and Nanotechnology, Singapore (M-H Tan MD); Yonsei Cancer Centre, Yonsei University College of Medicine, Seoul, South Korea (Prof S-Y Rha MD); Department of Oncology, Aarhus University Hospital, Aarhus, Denmark (F Donskov MD); University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA (N Agarwal MD); Vancouver Cancer Center, British Columbia Cancer Agency, Vancouver, BC, Canada. (C Kollmannsberger MD); Cross Cancer Center, University of Alberta, Edmonton, AB, Canada (S North MD); Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH, USA (Prof B I Rini MD); and Tom Baker Cancer Center, University of Calgary, Calgary, AB, Canada (D Y C Heng MD)

Summary

Background—The advent of targeted therapies in the past 7 years has extended median survival for metastatic renal-cell carcinoma. This improvement in clinical outcome has created a need for new, more accurate prognostic measures. We assessed the use of conditional survival—a measure that accounts for elapsed time since treatment initiation—for prognostication in patients with metastatic renal-cell carcinoma treated with first-line VEGF-targeted therapies.

Methods—We obtained data for patients with metastatic renal-cell carcinoma who were treated with a first-line VEGF-targeted therapy between April 7, 2003, and Oct 12, 2010, from our large multi-institutional International mRCC Database Consortium (centres in Canada, the USA, Singapore, Denmark, and South Korea). All histologies, performance statuses, and prognostic risk groups were included. The primary outcome was 2-year conditional survival, defined as the probability of surviving an additional 2 years from a given timepoint since the start of targeted

Correspondence to: Dr Toni K Choueiri, Kidney Cancer Center, Dana-Farber Cancer Institute/Brigham and Women's Hospital and Harvard Medical School, 450 Brookline Avenue, Boston, MA 02215 (DANA 1230), USA, toni_choueiri@dfci.harvard.edu.

*These authors contributed equally

Contributors

LCH, WX, DYCH, and TKC led to the writing of the paper. All authors contributed to study design, collection and assembly of data, or data analysis and interpretation. All authors reviewed and approved the final draft of the paper.

Conflicts of interest

WX, M-HT, and NA declare that they have no conflicts of interest.

therapy. Secondary analyses included 1-year and 3-year conditional survival, along with stratification of patients by Heng prognostic risk criteria and Karnofsky performance score, and conditional survival based on length of time on therapy. We used the Kaplan-Meier method and a landmark analysis to calculate conditional survival.

Findings—In the 1673 patients analysed, median follow-up for alive patients was 20·1 months (IQR 9·0–34·4). We recorded an increase in the 2-year conditional survival probability from 44% (95% CI 41–47) at 0 months to 51% (46–55) at 18 months since beginning targeted therapy. When stratified by the Heng prognostic risk criteria defined at therapy initiation, 2-year conditional survival changed little in the favourable and intermediate groups, but in the poor-risk group, 2-year conditional survival improved from 11% (8–15) at 0 months to 33% (18–48) after 18 months. When conditioned on time on targeted therapy from 0 months to 18 months, 2-year conditional survival improved from 44% (41–47) to 68% (60–75) in the overall population and from 74% (68–79) to 90% (77–96) in the favourable group, 49% (45–53) to 57% (45–67) in the intermediate group, and 11% (8–15) to 73% (43–89) in the poor risk group.

Interpretation—Conditional survival is a clinically useful prediction measure that adjusts prognosis of patients with metastatic renal-cell carcinoma on the basis of survival since treatment initiation or therapy duration. Conditional survival might be especially relevant to adjust prognosis for poor-risk patients.

Funding—The Trust Family Fund for Kidney Cancer Research.

Introduction

With rare exceptions, metastatic renal-cell carcinoma is generally incurable. More than 60000 patients are diagnosed and about 13500 patients die from advanced renal-cell carcinoma every year.¹ In the past 7 years, major advances have been made in the improvement of clinical outcome with the introduction of agents that target the hypoxia-inducible factor axis. More than 80% of patients achieve clinical benefit in the form of objective response to treatment or disease stabilisation with these drugs. Additionally, median overall survival with the targeted therapies is now greater than 2 years, which is a more than doubling in overall survival since the interferon- α era.^{2–6}

Survival estimates for patients with renal-cell carcinoma are guided by data from large randomised controlled trials and prognostic nomograms of clinical factors.^{3,7,8} These nomograms incorporate clinical criteria such as performance status and time from diagnosis to initiation of systemic therapy, and laboratory factors such as low haemoglobin and high lactate dehydrogenase concentrations, corrected calcium concentrations, and neutrophil and platelet counts. Striking differences in survival are seen with regard to the number of poor prognostic factors a patient has at the time they begin first-line treatment where patients with no risk factors live much longer. In patients who have no poor-risk factors, median overall survival was 20 months in the interferon- α era, but has improved to more than 3 years with the advent of VEGF-targeted therapies.^{3,7,8} Median overall survival of patients with intermediate risk (one to two risk factors) has increased from 10 months to 26 months with the use of targeted therapies. Although poor outcomes persist for patients in the poor-risk group (three or more risk factors), median overall survival for such patients has improved from 4 months with interferon α to 9 months with VEGF inhibitor treatment.^{3,7,8}

Survival projections made at diagnosis, which are often poor, can be disheartening for patients. Although predictions are clinically useful for directing therapy selection and end-of-life planning, they might lose their accuracy once a patient surpasses the predicted milestone. A question some times posed by patients is whether having outlived the median progression-free survival for a given agent means he or she will live longer. At this juncture,

physicians have little guidance on how to counsel patients who wish to revisit the prognosis discussion. The ability to adjust estimates on the basis of time elapsed since starting therapy would be clinically meaningful. Conditional survival, defined as the probability of surviving an additional amount of time after the patient has already survived a specific period of time, can provide this practical information. It accounts for the length of survivorship and changes in hazard rates over time. Conditional survival can provide more relevant prognostic information once a patient reaches or exceeds a specific landmark time of survival. It is a clinically powerful measure that can dynamically adjust prognosis as months and years pass and can aid substantially in the counselling of subsequent treatment decisions, improve patients' awareness and mental health, and better prepare patients for end-of-life decisions.

Conditional survival has been assessed in many other malignancies, including breast, colon, gastric, lung, and brain tumours.^{9–20} In renal-cell carcinoma, conditional survival has been assessed by two surgical series.^{21,22} Findings from these studies showed substantial improvements in outcome the longer the disease-free interval from surgery went on, and also showed dynamically improved survival even after adjustment for known prognostic criteria such as the American Joint Committee on Cancer's Tumour, Node, Metastasis (TNM) stage, Fuhrman grade, and tumour size. For example, 5-year survival of patients immediately after nephrectomy was 74.2%, which increased to 80.4% at 1 year, to 85.1% at 2 years, and to 90.6% at 5 years after nephrectomy.²² These studies surmised that the consideration of length of survivorship improves the accuracy of prognosis estimates and allows continual adjustment to surveillance plans. Both studies were done in the surgical setting; to our knowledge, no data have been reported for patients with advanced metastatic renal-cell carcinoma who are receiving systemic therapy.

To examine the use of conditional survival for prognosis in patients with metastatic renal-cell carcinoma treated with first-line VEGF-targeted therapy, we analysed data from our large, international, multi-institutional database. We assessed how outcome dynamically changes on the basis of previous survival and duration of targeted therapy and adjusted the findings for validated clinical prognostic criteria.

Methods

Study population

The International mRCC Database Consortium is a group of academic institutions from Canada, the USA, Singapore, Denmark, and South Korea. Data collection started in Aug 15, 2008, and the database closed for this analysis on Jan 14, 2011. As of January, 2011, the database included 1702 patients with mRCC from 16 centres. Patients are included in the database if they have advanced or metastatic renal-cell carcinoma. All histologies and types of systemic therapies are permitted. For this study, we included 1673 patients of all ages with metastatic renal-cell carcinoma who received a first-line VEGF-targeted therapy between April 7, 2003, and Oct 12, 2010. We excluded patients who received front-line mTOR inhibitors (n=27) or did not have complete treatment data (n=2).

To ensure consistent data collection, we collected baseline demographic, clinical, and laboratory data, including those previously known to have prognostic value, for all patients using uniform database templates. We standardised laboratory values against the institutional upper and lower limits of normal values. Survival data were collected from patients' medical records or publically available records. Local institutional review board approval was obtained from each centre.

The Heng or International mRCC Database Consortium prognostic model is a prognostic method that reflects the outcomes of patients who have been treated with VEGF-targeted

therapies. This model has been increasingly used in trials of novel agents.⁷ To identify whether conditional survival enhanced this known nomogram, we assessed the 2-year conditional survival based on the Heng risk groups as well as on individual prognostic risk factors such as Karnofsky performance scores (KPS).

Statistical analysis

The primary outcome was 2-year conditional survival, defined as the probability of a patient surviving an additional 2 years from each timepoint, conditioned on whether that patient had already survived that amount of time since the start of the first-line VEGF-targeted therapy. The secondary outcome was 2-year conditional survival, conditioned on length of time on targeted therapy. We explored the 1-year and 3-year conditional survival as secondary analyses. We analysed conditional survival using a landmark analysis approach calculated on the set of patients alive or receiving targeted therapy at 3 months since initiation of targeted therapy, and using 3-month increments for up to 18 months. These timepoints were defined before the study began, and were chosen because they were likely to coincide with the routine radiographic assessment of patients who receive targeted therapy and the subsequent prognosis and treatment discussions.

We measured survival times from the landmark timepoints until death or censored them at date of last follow-up. For example, conditional survival for the 3-month landmark set the time zero at 3 months from beginning of therapy and we used only those patients still alive at 3 months to estimate overall survival from that timepoint. We excluded data from patients who died before the landmark time or whose follow-up interval was less than the landmark time.

For conditional survival conditioned on time on targeted therapy, we excluded data for patients who discontinued treatment before the landmark time. For example, for 2-year conditional survival based on time on targeted therapy at 9 months, only patients who were on the initial targeted therapy for 9 months or longer were included in the analysis, and the 2-year conditional survival is the probability of surviving 2 additional years from that 9-month timepoint.

We estimated overall survival using the Kaplan-Meier product-limit method for all patients, stratified by Heng prognostic groups and KPS defined at therapy initiation; comparisons between groups were done with the log-rank test. We considered a two-sided p value of less than 0.05 to be statistically significant. We used SAS (version 9) for all statistical analyses.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The VEGF inhibitors given to the 1673 eligible patients included sunitinib, sorafenib, bevacizumab, pazopanib, and axitinib (table 1). 886 (53%) of these patients started their initial targeted therapy between 2003 and 2006, and 787 (47%) began treatment between 2007 and 2010. Most patients had had a previous nephrectomy, and less than a third had received immunotherapy (table 1). Most patients were men and had a good performance status, more than one site of metastasis, and clear cell histology (table 1).

The cutoff date for data analysis was Jan 14, 2011. At the time of analysis, 1378 patients (82%) had stopped their first-line VEGF-targeted therapy. Median overall survival after

beginning VEGF-targeted therapy was 20.2 months (95% CI 18.6–22.0; figure 1), with 714 (43%) patients remaining alive at data cutoff as of Jan 14, 2011. Median time on first-line VEGF-targeted therapy was 7 months (range 0–53). Median follow-up time in alive patients was 20.1 months (IQR 9.0–34.4). When we calculated follow-up with the inverse Kaplan-Meier curve, median follow-up time in all patients was 30.8 months (<1 to 78.7), although it should be noted that because more than 50% of patients have died, this method can result in an overestimation.

In this group of 1673 patients, the 2-year conditional survival increased over time from 44% (95% CI 41–47) initially to 51% (46–55) when conditioned on having survived up to 18 months after initiation of therapy, regardless of whether they still were on the first line VEGF-targeted therapy (table 2). When patients were stratified by the Heng prognostic risk criteria, probability of survival changed little with increasing time survived for individuals with a favourable or intermediate prognosis, but increased for those with a poor prognosis (table 2, figure 2). When stratified by performance status (KPS ≥80% and KPS<80%), patients with a high KPS had a greater 2-year conditional survival at any timepoint than did those with a low KPS (log-rank test $p<0.0001$ for difference at all timepoints; figure 2). The 2-year conditional survival from 0 months to 18 months for patients with a high KPS reached a low at 9 months following therapy initiation of 50% (46–54) to a high of 54% (48–59) at 18 months. For patients with poor KPS, 2-year conditional survival ranged from 19% (15–24) at 0 months to 33% (20–46) at 18 months (figure 2).

1-year conditional survival ranged from 66% (95% CI 64–69) initially to 70% (66–73) after surviving 18 months since the beginning of therapy. 3-year conditional survival reached a low of 31% (26–37) following 15 months and a high of 34% (30–37) following 6 months since the beginning of therapy (appendix).

For the analysis of conditional survival based on time on targeted therapy, we included only the patients who were alive and still on the initial VEGF-targeted therapy at each 3-month timepoint. Patients were excluded from analysis at each timepoint if they had discontinued the drug by that time. The 2-year conditional survival improved at each timepoint (month 0 through 18; table 3) initially at 44% (95% CI 41–47) to 68% (60–75) after 18 months on targeted therapy. When stratified by the Heng prognostic risk criteria, 2-year conditional survival increased in all risk categories (table 3, figure 2), with the greatest improvements seen in the poor-risk group. When stratified by performance status, 2-year conditional survival at any timepoint was statistically significantly greater in the high-KPS group than it was in the low-KPS group ($p<0.001$ for comparisons at all timepoints; figure 2). The 2-year conditional survival consistently increased in both groups from 0 months to 18 months from 53% (50–56) to 73% (64–79) in the patients with a high KPS patients and from 19% (15–24) to 42% (22–62) in patients with a low KPS (figure 2).

The 1-year and 3-year conditional survival probability improvements were greatest the longer patients are able to stay on the targeted therapy: the 1-year conditional survival steadily improved from 66% (64–69) at treatment initiation up to 85% (80–89) at 18 months, and the 3-year conditional survival increased from 32% (29–35) at treatment initiation to 48% (37–59) at 18 months (appendix).

The Heng risk criteria retained their prognostic value whether conditioned on previous survival time or on time on targeted therapy, up to 18 months ($p<0.0001$ for all comparisons; tables 2 and 3, figure 3).

Our series included 10% of patients with non-clear cell histologies. The 2-year conditional survival in patients with non-clear cell pathology steadily increased from 31% (95% CI 23–

40) at initiation therapy to 45% (31–58) if the patient survived 12 months and 56% (36–71) if the patient survived 18 months after beginning therapy.

Discussion

Our results show that, for patients with metastatic renal-cell carcinoma undergoing first-line VEGF inhibitor treatment, a longer survival interval and duration on therapy up to 18 months after beginning targeted therapy increases survival probability. For example, in our series, patients who were alive at 18 months after beginning therapy (irrespective of whether they remained on first-line VEGF-targeted therapy), had a 51% probability of being alive an additional 2 years from that 18 month timepoint. Unadjusted for clinical prognostic factors, this projection had increased from a 44% probability of living 2 years more in all patients at the time of treatment initiation. Conditional survival further demonstrates the clear differences in survival between clinical prognostic groups. If a patient had a favourable risk at initiation of targeted therapy and was alive at 18 months, his or her probability of surviving an additional 2 years from that 18-month timepoint was 69% compared with 33% for those with a poor prognosis.

We know of no other prognostic measure in metastatic renal-cell carcinoma that takes into account length of survivorship and duration of therapy (panel). Additionally, our findings suggest that the use of conditional survival can enhance accepted prognostic nomograms such as the Heng criteria. Past work in other cancers has shown that survival projections based on initial prognostic measures can converge the longer a patient survives.^{17,20} This convergence implies that important prognostic criteria at diagnosis might become less valuable as time lapses. By contrast with those findings, our findings suggest that the Heng risk group prognostication retained its value over time from 3 months to 18 months ($p<0.0001$ in all comparisons; figure 2), but that there was a trend to convergence in patients with poor risk who remained on first-line targeted therapy for long periods of time.

Of the 117 patients in the poor risk group who survived up to 12 months, 70% had stable disease or better (a 70% disease control rate; DCR) on first-line targeted therapy, which was similar to a 78% DCR in patients with favourable risk and an 80% DCR in patients with intermediate risk who survived the same amount of time. In the 54 poor-risk patients who survived for more than 18 months, DCR was 78% and median duration on first-line therapy was 14 months and on second-line therapy was 5.5 months. These durations were very close to those for patients from the more favourable risk groups surviving to the same landmark times (DCR 80% and 84%; median time on the first-line targeted therapy 16.6 months and 15 months; median time on second-line targeted therapy 6.2 months and 5.5 months, respectively, for the favourable and intermediate groups). By contrast with those findings, in all patients from the start of therapy, the poor-risk group had a DCR of 43% and a very short median duration of 3.8 months on initial targeted therapy—the corresponding measurements in the intermediate-risk group were 66% and 8 months and in the favourable-risk group were 76% and 12.9 months. These results show that poor-risk patients can respond to VEGF-targeted therapy and that when they do respond, their outcomes can be similar to those of patients with favourable and intermediate risk and suggests that the incorporation of conditional survival into survival projections enhances the Heng prognostic measure, especially in patients in the poorest risk groups. However, only a small subset of patients in the poor-risk group survived for more than 1 year. Therefore, the poor-risk patients assessed at later time points might not be representative of the whole poor-risk population analysed at treatment initiation.

Our data also draw attention to the effect of performance status on outcome. Patients with a KPS of less than 80% had statistically significantly lower survival probabilities at any given

timepoint (figure 2). KPS was established only at the start of treatment and was not adjusted at each timepoint. Although an element of the Heng prognostic risk group score, KPS was also an independent prognostic factor.⁷ As with the risk groups and conditioned on survival alone, this risk showed a trend to convergence the longer a patient with a low performance status lived, but was stable for patients with high performance status. Patients with a low performance status are generally excluded from clinical trials and conditional survival enhances our prognostication in this understudied population of patients.

Notably, the risk-group convergence from poor to favourable occurred only in patients who remained on targeted therapy at later timepoints and was not as pronounced in patients who were simply survivors—those alive on a subsequent therapy or observation such as those having indolent disease (tables 2 and 3). Thus, the improvement in survival can probably not be attributed simply to more indolent disease—it might be most attributable to treatment-responsive disease, differences in the disease biology, and unmeasured or unknown predictive factors. That the greatest improvement occurred in the patients with poor risk further draws attention to the fact that these patients can have disease that is responsive to VEGF-inhibitor treatment. In theory, this unexpected responsiveness could also be due to some favourable biological differences not captured by known clinical factors, that enhanced their responsiveness to treatment. Clinically, this finding is important because patients with such unfavourable prognoses have been understudied in most targeted therapy registration trials with the exception of temsirolimus.²³

Much of evidence-based medicine is based on extrapolation of outcomes from randomised controlled trials, but this practice is limited by the fact that fewer than 10% of patients are enrolled on clinical trials and that study patients tend to be a select, relatively healthy group with mostly good performance status and clear cell histologies compared with an all-comer clinic population. Patients with non-clear cell histologies are often excluded from clinical trials but comprise 10–15% of all renal-cell carcinoma diagnoses. With the exception of temsirolimus,²³ data for the effect of VEGF-targeted therapies in non-clear cell disease is restricted to small phase 2 studies and retrospective series. Until a phase 3 trial is done including patients with non-clear cell disease, population-based studies such as this one can provide insight into outcome after treatment with available agents.

Limitations of this study include the absence of adjustment for subsequent treatments—which might affect overall survival—and exclusion of patients who had non-VEGF-targeted treatments such as the mTOR inhibitors temsirolimus and everolimus. We acknowledge that the mTOR inhibitors are widely used in the treatment of renal-cell carcinoma.^{23,24}

Temsirolimus is the only approved targeted therapy with randomised control trial data showing clinical benefit specifically in poor-risk patients and a statistically significant overall survival advantage, albeit of 3 months. Because the poor-risk population benefited most from continuous adjusted prognostication with our conditional survival measure, its use should be assessed in patients treated with mTOR inhibitors.

In addition to the potential incorporation of this prognostic measure into clinical practice, integration into future research and large-scale clinical trials should be considered. Conditional survival analysis of existing datasets from large randomised controlled trials in metastatic renal-cell carcinoma might alter how we interpret their static end points. In the clinic, this idea could be applied further in different clinical scenarios for which fewer prospective data about efficacy are available, such as the survival benefit of post-cytoreductive nephrectomy and outcome with second-line or third-line targeted therapies. In each of these settings, the measure should adjust for subsequent and previous treatments. The Heng prognostic criteria have been validated as remaining relevant at the start of

second-line targeted therapy,²⁵ and the incorporation of conditional survival might provide additional information to enhance clinical decision making.

Inherent to any retrospective work is missing data; in our study only two of the 1675 patients treated with first-line VEGF inhibitors were eliminated for absence of treatment information. The Heng prognostic criteria were not available for about 10% of the population because of missing KPS or specific laboratory measurements. Other patient characteristics in table 1 and treatment duration were generally well balanced between the groups of patients that had full prognostic criteria data and those with some missing data ($p < 0.05$), except that the group with missing data was more likely to have only one metastatic site before nephrectomy (although the difference was less than 10%). Therefore, survival bias because of missing prognostic data is expected to be minimal in this population. We recognise that survival estimates at 12 months and beyond were made on the basis of data from small sample sizes, which prohibit definitive conclusions about the validity of those later-year trends. Finally, all our calculations were done within one database; external validation of this measure is important before it is uniformly accepted into clinical practice.

Our findings show that survival probability in metastatic renal-cell carcinoma is dynamic and directly dependent on time elapsed from treatment initiation and duration of therapy. Conditional survival can be a valuable measure permitting more accurate prognostication for clinicians and patients as they discuss survival expectations, subsequent treatment decisions, and end-of-life planning. It could be most useful for patients with poor risk or a poor performance status and in all patients who surpass their expected median overall survival estimated on the basis of projections at diagnosis or treatment initiation.

Acknowledgments

This is a project of the International mRCC Database Consortium. We are indebted to our patients without whom this study could not be accomplished. We greatly appreciate the assistance of our colleagues at our respective centres, who also contributed patient information, and are especially grateful for the efforts of our data managers and study coordinators.

LCH has a consultant or advisory role at Novartis and Pfizer and has received research funding from Bristol-Myers Squibb, Novartis, and Genentech. GAB has a consultant or advisory role at and has received honoraria and research funding from Pfizer. JJK has a consultant or advisory role at Aveo and and has received research funding from Pfizer. MM has a consultant or advisory role at and has received research funding from Novartis and Pfizer. LW has a consultant or advisory role at Pfizer and Novartis and has received research funding from Pfizer, Novartis, and GlaxoSmithKline. SS has a consultant or advisory role at Pfizer, Novartis, and Genentech. UNV has received honoraria and research funding from Pfizer, Novartis, and GlaxoSmithKline. S-YR has a consultant or advisory role at Novartis, Pfizer, and GlaxoSmithKline, and has received research funding from Novartis and Bayer Korea. FD has received research funding from Novartis. CK has a consultant or advisory role at and has received honoraria and research funding from Pfizer, Novartis, and GlaxoSmithKline. SN has a consultant or advisory role at Pfizer, Novartis, Bayer, and GlaxoSmithKline. BIR has a consultant or advisory role at Pfizer, GlaxoSmithKline, Aveo, and Bayer/Onyx, and has received research funding from GlaxoSmithKline and Pfizer. DYCH has a consultant or advisory role at Pfizer, Novartis, and Bayer/Onyx. TKC has received research funding from Pfizer and has a consultant or advisory role at Aveo, Pfizer, Novartis, GlaxoSmithKline, Genentech, and Bayer/Onyx.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin.* 2012; 62:10–29. [PubMed: 22237781]
2. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol.* 2010; 28:2144–2150. [PubMed: 20368553]

3. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol.* 2002; 20:289–296. [PubMed: 11773181]
4. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2009; 27:3584–3590. [PubMed: 19487381]
5. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol.* 2010; 28:2137–2143. [PubMed: 20368558]
6. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol.* 2010; 28:1061–1068. [PubMed: 20100962]
7. 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; 27:5794–5799. [PubMed: 19826129]
8. 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; 17:2530–2540. [PubMed: 10561319]
9. Choi M, Fuller CD, Thomas CR Jr, Wang SJ. Conditional survival in ovarian cancer: results from the SEER dataset 1988–2001. *Gynecol Oncol.* 2008; 109:203–209. [PubMed: 18329082]
10. Christensen LH, Engholm G, Ceberg J, et al. Can the survival difference between breast cancer patients in Denmark and Sweden 1989 and 1994 be explained by patho-anatomical variables?—a population-based study. *Eur J Cancer.* 2004; 40:1233–1243. [PubMed: 15110888]
11. Davis FG, McCarthy BJ, Freels S, Kupelian V, Bondy ML. The conditional probability of survival of patients with primary malignant brain tumors: surveillance, epidemiology, and end results (SEER) data. *Cancer.* 1999; 85:485–491. [PubMed: 10023719]
12. Fuller CD, Wang SJ, Thomas CR Jr, Hoffman HT, Weber RS, Rosenthal DI. Conditional survival in head and neck squamous cell carcinoma: results from the SEER dataset 1973–1998. *Cancer.* 2007; 109:1331–1343. [PubMed: 17326199]
13. Henson DE, Ries LA, Carriaga MT. Conditional survival of 56,268 patients with breast cancer. *Cancer.* 1995; 76:237–242. [PubMed: 8625098]
14. Janssen-Heijnen ML, Houterman S, Lemmens VE, Brenner H, Steyerberg EW, Coebergh JW. Prognosis for long-term survivors of cancer. *Ann Oncol.* 2007; 18:1408–1413. [PubMed: 17693654]
15. Merrill RM, Henson DE, Barnes M. Conditional survival among patients with carcinoma of the lung. *Chest.* 1999; 116:697–703. [PubMed: 10492274]
16. Merrill RM, Henson DE, Ries LA. Conditional survival estimates in 34,963 patients with invasive carcinoma of the colon. *Dis Colon Rectum.* 1998; 41:1097–1106. [PubMed: 9749492]
17. Moller MB, Pedersen NT, Christensen BE. Conditional survival of patients with diffuse large B-cell lymphoma. *Cancer.* 2006; 106:2165–2170. [PubMed: 16586498]
18. Skuladottir H, Olsen JH. Conditional survival of patients with the four major histologic subgroups of lung cancer in Denmark. *J Clin Oncol.* 2003; 21:3035–3040. [PubMed: 12915592]
19. Wang SJ, Emery R, Fuller CD, Kim JS, Sittig DF, Thomas CR. Conditional survival in gastric cancer: a SEER database analysis. *Gastric Cancer.* 2007; 10:153–158. [PubMed: 17922092]
20. Zamboni BA, Yothers G, Choi M, et al. Conditional survival and the choice of conditioning set for patients with colon cancer: an analysis of NSABP trials C-03 through C-07. *J Clin Oncol.* 2010; 28:2544–2548. [PubMed: 20406942]
21. Thompson RH, Leibovich BC, Lohse CM, et al. Dynamic outcome prediction in patients with clear cell renal cell carcinoma treated with radical nephrectomy: the D-SSIGN score. *J Urol.* 2007; 177:477–480. [PubMed: 17222614]
22. Karakiewicz PI, Suardi N, Capitanio U, et al. Conditional survival predictions after nephrectomy for renal cell carcinoma. *J Urol.* 2009; 182:2607–2612. [PubMed: 19836798]
23. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007; 356:2271–2281. [PubMed: 17538086]

24. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008; 372:449–456. [PubMed: 18653228]
25. Heng DY, Xie W, Bjarnason GA, et al. A unified prognostic model for first- and second-line targeted therapy in metastatic renal cell carcinoma (mRCC): results from a large international study. *Proc Am Soc Clin Oncol*. 2010; 28(suppl 15) abstr 4523.

Panel: Research in context**Systematic review**

We searched PubMed for conditional survival studies in renal-cell carcinoma and other malignancies as well as for statistical design with the following search terms: “conditional survival”, “conditional survival renal cell carcinoma”, “conditional survival cancer”, “conditional survival malignancy”, and “conditional survival VEGF targeted therapy”. We reviewed studies that assessed conditional survival in different cancers. Only two studies assessing conditional survival in renal-cell carcinoma have been reported,^{21,22} and they were done in the surgical setting. We used our large international, multi-institutional database to examine the effect of conditional survival in patients with metastatic renal-cell carcinoma treated with first-line VEGF-targeted therapies. Our goal was to assess how outcome dynamically changes based on previous survival and duration of therapy and to adjust findings for validated clinical prognostic criteria.

Interpretation

We know of no other study to systematically assess conditional survival in patients with metastatic renal-cell carcinoma treated with targeted therapies. Our findings show that the survival probability in metastatic renal-cell carcinoma is dynamic and directly dependent on time elapsed from treatment initiation and duration of therapy. Conditional survival also enhanced known prognostic criteria such as the Heng prognostic model. It might add the most prognostic value in patients with poor risk and a poor performance status, and in all patients who surpass their expected median overall survival estimated on the basis of projections made at diagnosis or the start of treatment. We believe that this measure will aid clinicians and patients in continual prognosis discussions and subsequent treatment decisions.

Figure 1. Kaplan-Meier analysis of overall survival since initiation of targeted therapy for all patients

Dotted lines are 95% CIs. Alive patients were censored at date of last follow-up.

Figure 2. Probability of surviving 2 additional years

KPS=Karnofsky performance score. Error bars are 95% CIs. Probability conditioned on time survived after initiation of targeted therapy and stratified by (A) Heng prognostic risk group and (B) KPS. Probability conditioned on time survived and on targeted therapy and stratified by (C) Heng prognostic risk group and (D) KPS defined at initiation therapy.

Figure 3. Kaplan-Meier analysis of overall survival stratified by Heng prognostic risk group defined at initiation of targeted therapy

Probabilities are conditioned on (A) survival at 3 months since treatment initiation (N=1316), (B) survival at 12 months since treatment initiation (N=808), (C) being alive and still on treatment after 3 months (N=1082), and (D) being alive and still on treatment at 12 months (N=414).

Table 1

Characteristics of patients at beginning of VEGF-targeted therapy (N=1673)

	n (%)
Age	
<60 years	767 (46%)
60 years	906 (54%)
Karnofsky performance score	
80%	1161 (69%)
<80%	424 (25%)
Unknown	88 (5%)
Sex	
Female	435 (26%)
Male	1238 (74%)
Number of metastases	
1	389 (23%)
>1	1280 (77%)
Unknown	4 (<1%)
Pathology	
Clear cell	1387 (83%)
Non-clear cell	157 (9%)
Unknown	129 (8%)
Sarcomatoid features	
No	1321 (79%)
Yes	127 (8%)
Unknown	225 (13%)
Previous nephrectomy	
No	341 (20%)
Yes	1332 (80%)
Previous immunotherapy	
No	1214 (73%)
Yes	459 (27%)
Type of therapy	
Sunitinib	1240 (74%)
Sorafenib	334 (20%)

	n (%)
Bevacizumab	96 (6%)
Pazopanib	2 (<1%)
Axitinib	1 (<1%)
Diagnosis to therapy <1 year	
No	832 (50%)
Yes	839 (50%)
Unknown	2 (<1%)
Heng risk group	
Favourable	290 (17%)
Intermediate	770 (46%)
Poor	441 (26%)
Unknown	172 (10%)

2-year conditional survival (conditioned on time survived regardless of whether still on the first-line targeted therapy) for all patients and stratified by Heng risk group

Table 2

	Overall		Stratified by Heng risk group [*]				p value
	Total/number died	2-year conditional survival (95% CI)	Favourable	Intermediate	Poor		
	Total/number died	2-year conditional survival	Total/number died	2-year conditional survival	Total/number died	2-year conditional survival	
0 months	1673/959	44% (41–47)	290/103	74% (68–79)	770/424	49% (45–53)	11% (08–15)
3 months	1468/805	45% (42–48)	280/100	72% (67–78)	707/383	48% (44–52)	13% (9–18)
6 months	1265/656	47% (43–50)	269/94	70% (63–75)	617/323	48% (43–52)	15% (10–21)
9 months	1080/544	46% (43–49)	248/84	68% (61–74)	528/272	47% (42–52)	14% (8–22)
12 months	915/437	48% (44–52)	228/70	71% (63–77)	463/235	46% (41–52)	20% (11–30)
15 months	784/349	50% (45–54)	213/61	70% (62–77)	404/194	46% (40–52)	24% (14–37)
18 months	667/276	51% (46–55)	199/54	69% (60–76)	346/158	45% (38–52)	33% (18–48)

* Excluded 172 patients whose prognostic risk was unknown at the start of therapy; p values are from the log-rank test with two degrees of freedom, which compares the survival distributions among the three groups (favourable, intermediate, and poor) at each landmark analysis.

Table 3

2-year conditional survival (conditioned on time on first-line targeted therapy) for all patients and stratified by Heng risk group defined at therapy initiation

Overall		Stratified by Heng risk group [*]						p value
Total/number died	2-year conditional survival (95% CI)	Favourable		Intermediate		Poor		
		Total/number died	2-year conditional survival	Total/number died	2-year conditional survival	Total/number died	2-year conditional survival	
0 months	1673/959	290/103	44% (41–47)	70/424	49% (45–53)	441/345	11% (8–15)	<0.0001
3 months	1204/620	249/82	51% (47–54)	594/314	52% (47–56)	239/166	16% (10–23)	<0.0001
6 months	843/378	202/57	56% (52–60)	427/206	55% (49–60)	128/74	24% (15–35)	<0.0001
9 months	615/247	170/42	59% (54–63)	308/140	54% (47–60)	78/37	33% (19–48)	<0.0001
12 months	453/156	137/26	64% (58–69)	228/91	55% (47–62)	49/20	47% (29–64)	<0.0001
15 months	361/113	111/16	65% (58–71)	188/73	54% (45–62)	35/12	59% (36–76)	<0.0001
18 months	268/73	89/10	68% (60–75)	134/46	57% (45–67)	21/6	73% (43–89)	<0.0001

* Excluded 172 patients whose prognostic risk was unknown at the start of therapy; p-values are from the log-rank test with two degrees of freedom, which compares the survival distributions among the three groups (favourable, intermediate, and poor) at each landmark analysis.