Reflections on the current knowledge of epidemiology, treatment and prognosis for renal cell carcinoma
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PROGNOSTIC MODELS AND FACTORS FOR PATIENTS WITH RENAL CELL CARCINOMA; A SURVEY ON THEIR USE AMONGST UROLOGISTS

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ABSTRACT

Purpose
To assess the use of prognostic factors and models in renal cell carcinoma (RCC) and to gain insight in the motivations precluding prognosis estimation and the use of prognosticators.

Materials and Methods
A questionnaire was send to 110 urologists involved in the CROES renal mass study. Frequencies were gathered using descriptive statistics.

Results
The majority of the 86 responders worked in a university hospital in Europe. Most of the urologists (97.7%) used the TNM classification and 44% performed prognosis estimations in all patients. Main reason not to estimate prognosis was lack of accuracy (20.9%) and of additional benefit (11.6%). Additionally clinical, laboratory or pathological factors were used by 89.5% of the urologists and biomarkers by 16.3%.

Preoperative models were utilized by 20.9%, postoperative models by 38.4% and metastatic models by 38.4%. The Raj and Motzer models were the most used in preoperative and metastatic settings while no predominance among the different postoperative models was seen. The most important reasons to skip the use of models were “lack of additional value” and “lack of familiarity” reported by 30.2% and 27.9% of the responders respectively.

Conclusions
The TNM is the mainstay for assessing prognosis in RCC. Our data indicates that penetration of prognostic systems is at the most moderate, suggesting limited use outside original developmental settings. On the contrary, clinical, laboratory and pathological factors are used by almost all urologists for prognosis estimations. The most important reason not to use models is the lack of additional value.

INTRODUCTION

The first TNM staging system for renal tumours was released in 1978. It is the standard staging classification for renal cell carcinoma (RCC) with the pathological stage being the mainstay to assess survival prognosis. Besides TNM, other factors that may influence prognosis in RCC have been identified. Clinical factors include symptoms at presentation by opposition to incidental diagnosis and ECOG performance status at diagnosis, laboratory parameters as thrombocytes and haemoglobin level and pathological factors as Fuhrman grade and the presence of tumour necrosis. Moreover, the discovery of the von Hippel-Lindau gene led to the description of several biomarkers involved in the pathogenesis of RCC and of possible prognostic significance.

In attempts to assess prognosis more accurately, prognostic systems and nomograms combining some of these factors have been developed for different settings in RCC. In preoperative prognostic models clinical and radiological factors are combined. Pathological and clinical factors are incorporated in postoperative models. Prognostic systems for metastatic RCC incorporate clinical and laboratory variables.

While internal validation is available for most of these models, external validation in different populations than the developmental one is essential prior to implementation and widespread use of a model or nomogram. Currently many prognostic integrated systems are available for RCC, however sound data about their use in clinical practice is lacking.

Primary objective of this study was to evaluate the use of prognostic factors and models in RCC among urologists. Secondary objective was to gather the negative motivations that preclude the use of prognosticators/prognostic models and to identify demographic factors associated with the use of models or biomarkers.

MATERIALS AND METHODS

Recruitment
A survey was conducted among the principal investigators of active centres participating in the Clinical Research Office of the Endourological Society (CROES) Renal Mass Study. A personalized questionnaire was distributed by e-mail between February 2011 and March 2012. Forms could be returned by email or fax. Three e-mail waves were sent and the inclusion closed in May 2012. No approval of the ethical committee was needed for this study.
Questionnaire
To confection the questionnaire a literature review was performed on prognostic models and factors. MeSH terms “prognosis, risk factor, survival, prognostic factor, model, nomogram, integrated staging system, validation, and calibration plot” were crossed each with “renal cell carcinoma”. Related key papers’ references were meticulously studied. Besides the TNM, other prognostic systems were selected based on introduction of original variables, description in high impact factor journals, presence of validation studies or high predictive accuracy. The prognostic systems selected for the questionnaire are displayed in Table 1 10-23.

The questionnaire contained 20 questions (Addendum 2) divided in 3 sections. The first section (6 questions) explored demographic and global data on prognosis estimation. The second section (7 questions) assessed the use of TNM and other clinical, laboratory, pathological parameters and markers. Section 3 (7 questions) contained questions on the use of other prognostic models and opinions on their usefulness.

Data for age and years as certified urologists (questions 1-2) was numerical; questions exploring absolute frequencies (1-5, 7-9 and 14) required a unique response. The rest of the questions were multiple choices and multiple responses could be chosen but for question 6 that assessed the most important reason to “not to estimate prognosis”. Questions 6 and 20 (“usefulness of prognostic models”) had space for free text.

Statistical analysis
The results were analysed using the descriptive statistics function of Predictive Analytics Software Statistics 18.0.2 (Armonk, New York, United States of America). Categorical variables were reported as numbers and percentages and continuous variables as median and range (non-parametric distribution).
Associations between demographic data and the use of models or markers were assessed with logistic regression (age, years as urologist) and Chi-square tests (number of treated patients, continent, use of markers and models). All tests were performed two-tailed and a p-value of 0.05 was considered statistically significant.

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome</th>
<th>Population</th>
<th>Variables</th>
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</thead>
<tbody>
<tr>
<td><strong>PREOPERATIVE SETTING</strong></td>
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<tr>
<td>Cindolo model [10]</td>
<td>recurrence risk</td>
<td>localized RCC</td>
<td>Symptomatic presentation, tumour size</td>
</tr>
<tr>
<td>Raj nomogram [12]</td>
<td>DFS</td>
<td>localized RCC</td>
<td>Gender, symptoms, radiological features: lymphadenopathy, necrosis and tumour size</td>
</tr>
<tr>
<td>Karakiewicz nomogram [13]</td>
<td>CSS</td>
<td>all stages RCC</td>
<td>Age, gender, symptoms, tumour size, T-stage status</td>
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<td><strong>POSTOPERATIVE SETTING</strong></td>
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<tr>
<td>Kattan nomogram [14]</td>
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<td>localized RCC</td>
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<td>UISS [15]</td>
<td>OS/CSS</td>
<td>all stages RCC</td>
<td>ECOG PS, TNM stage and Fuhrman grade</td>
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<td>SSIGN [16]</td>
<td>CSS</td>
<td>all stages clear cell RCC</td>
<td>TNM stage, tumour size, Fuhrman grade and tumour necrosis</td>
</tr>
<tr>
<td>Karakiewicz nomogram [17]</td>
<td>CSS</td>
<td>all stages RCC</td>
<td>Symptoms, TNM stage, tumour size, Fuhrman grade</td>
</tr>
<tr>
<td>Klatte nomogram [18]</td>
<td>DFS</td>
<td>localized clear cell RCC</td>
<td>ECOG PS, T-stage and markers (Ki-67, p53, endothelial VEGFR-1, epithelial VEGFR-1, and epithelial VEGF-D)</td>
</tr>
<tr>
<td>Kim model [19]</td>
<td>CSS</td>
<td>all stages clear cell RCC</td>
<td>ECOG PS, T-stage, metastatic status, and markers (p53, CA9, and vimentin)</td>
</tr>
<tr>
<td><strong>METASTATIC SETTING</strong></td>
<td></td>
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</tr>
<tr>
<td>Motzer model [20]</td>
<td>OS</td>
<td>mRCC patients undergoing systemic treatment</td>
<td>Karnofsky PS, LDH, haemoglobin, calcium, prior nephrectomy</td>
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<tr>
<td>Heng model [21]</td>
<td>OS</td>
<td>mRCC patients undergoing VEGF targeted therapy</td>
<td>Karnofsky PS, haemoglobin, calcium, neutrophils, platelets, time to diagnosis</td>
</tr>
<tr>
<td>Choueiri model [22]</td>
<td>progression free survival</td>
<td>mRCC patients undergoing VEGF targeted therapy</td>
<td>ECOG PS, calcium, neutrophils, platelets, time to diagnosis</td>
</tr>
<tr>
<td>Kim model [23]</td>
<td>CSS</td>
<td>clear cell mRCC patients</td>
<td>ECOG PS, T-stage and markers (CAIX, PTEN, vimentin, p53)</td>
</tr>
</tbody>
</table>

Table 1. Brief description of the outcomes, developmental population and variables included in the prognostic models and nomograms included in our survey. DFS- disease free survival, OS- overall survival, CSS- cancer specific survival, mRCC - metastatic RCC, cT stage- clinical T-stage, PS- performance status
RESULTS

From 110 active centres of the CROES Renal Mass Study 86 (78.2%) questionnaires were returned and included in the analyses. All responders were certified urologists.

Demographic data of the responders is displayed in Table 2. Most important reasons to skip prognostic estimation are illustrated in Figure 1.

Table 3 shows frequencies on the use of the TNM staging and other models for prognosis estimation. Overall 39 responders (45.3%) did not utilize other prognostic models than the TNM. Motivations not to use other models were: “too little additional value” and “not being familiar with the model” indicated by 26 (30.2%) and 24 (27.9%) responders respectively.

![Figure 1. Reasons for urologists to skip prognosis estimation in RCC patients (question 6). The numbers within the figure correspond to the number of responders who selected the answer and the percentages are calculated over the total responders. The percentages mentioned on the y-axis are calculated over the number of urologists who answered this question in the survey (n=40). According to the survey this question was exclusive for those that estimate prognosis.](image-url)

Table 2. Demographic data of the responders (questions 1-3), number of patients with RCC seen per year and urologist (question 4) and proportion of patients in which prognosis estimation is done (question 5).

Table 4 shows the frequencies of use for the factors mentioned in our survey. Molecular markers were utilized by 14 (16.3%) of the responders. Among them VEGF(R) was the most frequently used marker by 15.1% of the responders (n=13), 9.3% used p53 (n= 8), 5.8% used CAIX and Ki-67 (n= 5 each) and 1.2% used Vimentin and p21 (n=1 each).
Table 3. Utilization of the TNM classification and other RCC prognostic models for prognosis estimation in RCC by urologists. (Questions 7,15-17) 1 4 urologists used 2 models; 1 used a model not specified in the questionnaire.

Table 4. Frequencies of use for clinical, laboratory and pathological factors for prognosis estimation in RCC by urologists (questions 8-11).

Table 5. Association (p-values) between the use of markers or models in RCC and demographic factors regarding the urologists.

DISCUSSION

We gathered information on current use of prognostic models and clinical / pathological factors of possible prognostic value in RCC by approaching a convenience sample, which consisted of principal investigators of the prospective CROES renal mass study (2010-2012), a contemporary registry on patterns of treatment of renal tumours24. In this way we aimed to ensure that the sample represented the target population: urologists treating RCC and familiar with prognostic models and factors related to the condition. In our sample the use of models or markers was not related to any demographic data concerning age of the responder and years or type of practice.
Prognostic estimation and the use of prognostic models

Our survey shows that the TNM classification is universally used in RCC. Furthermore 44% and 24.5% of the urologists estimates prognosis in all and most of the RCC cases respectively. This data confirms the excellent penetration of the TNM classification whether as clinical tool in treatment decision\textsuperscript{2,3} or as predictor system. The pathological TNM is not only a powerful predictor for cancer specific survival with accuracy of 85%\textsuperscript{25} and may drive the opportunity for adjuvant survival management in the future\textsuperscript{25,26}, but is also helpful in designing follow-up schemes. Besides general acquaintance with the TNM classification, as oldest in use, present results support its “friendly use” and generality\textsuperscript{27}.

However, there is a discrepancy between the rate of responders that acknowledge estimating prognosis and the figures on the use of the TNM. The prognostic value of the TNM seems to be somehow underestimated or forgotten as less than half of the responders estimate prognosis in all cases. Although this figure is upgraded to 69% when including those that estimate prognosis in most of the cases, still one third of the responders might consider the TNM as a mere classification and associate prognosis estimation with the use of other prognostic systems than the TNM.

Preoperative prognostic systems using only clinical and radiological factors were marginally utilised by our responders. Usefulness of preoperative models is a matter of debate. Preoperative determination of recurrence risk or survival is not likely to influence the treatment decision that mainly depends on clinical TNM stage and patient characteristics\textsuperscript{2,3}. Moreover prognosis estimations with postoperative data is equally or more accurate than preoperative estimation\textsuperscript{50-13}. Nevertheless in the current interventional scenario a certain number of patients with small renal masses treated by ablation or surveyed may still benefit on the use of these preoperative models as not definitive pathology, based on surgical specimen, will be available to properly staging tumours\textsuperscript{11}.

Our survey indicates a moderate penetration of postoperative models, although there was no clear preference for any model. Survival outcomes, patient population and performance, mostly expressed as concordance -indexes, (c-indexes) among these models and their external validation studies differ widely in the literature\textsuperscript{14-17}. The c-index of the 2002 TNM ranges from 0.746-0.848 for the T- stage\textsuperscript{13,18,25}. Until date only few models have shown a higher c-index in other settings than their developmental one\textsuperscript{28}. Furthermore validation has either failed or is not available for some. On internal validation an accuracy of 1.0 meaning perfect prediction, is never expected. However to provide incremental value to the TNM classification, the existing models should approach an accuracy of 0.9 on external validation, which none currently do\textsuperscript{8}.

Use of prognostic models in metastatic RCC

The use of prognostic models in metastatic setting was moderate (38.4%). The professional profile of the sample, exclusively urologists, may be the explanation. Although the number of cases of metastatic RCC seen by individual/year was not recorded it might be relatively low and likely a survey focusing on oncologists would have shown different results. The figure hereby presented may be discussed under two different perspectives. For those countries where Uro-oncologists are entitled to medically treat metastatic RCC, this figure is a pessimistic one as risk prognostic assessment in metastatic RCC is of outmost importance to determine treatment. Conversely for those countries where metastatic RCC is directly under supervision of Onco-urological specialists the figure shows a non-negligible interest of urologists in metastatic RCC prognostic estimation. The authors consider that country based surveys on this specific point would provide a better answer. As expected the Motzer model was by far the most frequently used in metastatic setting\textsuperscript{20}. The accuracy of this model ranges from 52 to 73% including some reports on VEGF targeted therapy\textsuperscript{8}. The Choueiri model\textsuperscript{22} for which no internal or external c-indexes are provided, was much lesser used.

Use of additional factors

Almost 90% of the urologists indicated to take clinical, laboratory and pathological parameters into account when estimating prognosis. Approximately 80% of the urologists used several of these factors and more than half also used 3 or more different factors of one category. Although the use of additional factors did not correlate with the use of other prognostic systems than the TNM, this data indicates a strong awareness of the urological community on the possible prognostic impact of symptoms, histological subtype and nuclear grade.

Although some studies reported Fuhrman grade, symptomatic presentation, ECOG performance status or age as independent predictors for survival, other factors as subtype, haemoglobin and thrombocytes level still show conflicting results\textsuperscript{4}. In spite of their frequent use no uniform interpretation for
risk of death or disease free survival (DFS) exists for these factors. A small percentage of urologists indicated to use markers for prognostic purposes. Their use as integrated model was negligible. It’s worth mentioning that recently a model integrating biomarkers has shown a high additional predictive value (c-index 0.904) for DFS in localized RCC\textsuperscript{18}. Besides the fact that most of the biomarkers models are of recent publication, the absence of consistent results on the value of individual markers as well as cost issues limit their current use as prognostic tools\textsuperscript{29}. Although the subject is the object of sharp research a longer period of time is necessary to assess the true impact of such models. Their generality will ultimately depend on their additional value when combined with other prognostic systems at use and their availability.

Reasons to skip prognostic estimation
The main reason to preclude prognosis estimation reported by half of the responders of this question was the lack of accuracy of the different prognostic systems/factors. Other reasons in decreasing order were lack of additional benefit, absence of clinical relevance and being time consuming. These opinions reflect the well-known concerns on the external performance of prognostic systems\textsuperscript{27,29} and open the door for a critical assessment on the developmental methodology of prognostic systems in cancer, on their usefulness in the current treatment practice in RCC and on their functionality.

In response to the more specific question on the reason for not using other models than TNM, again most important reason was lack of additional value and one third of the urologists indicated that not being familiar with models was the reason not to use them. Seeing that the questionnaire was spread among research minded urologists, the actual number of urologists who are not familiar with prognostic systems will likely be higher.

Limitations
The limitations of our study include: models selection, population sample and geographical distribution of the responders. Not all the models described in the literature were included in our survey. Inclusion of all reported models will have lengthened the questionnaire and most likely decreased the response rate, which was higher than expected in this kind of surveys. The convenience sample was dictated by the focused practice. In fact it is impossible to assess the potential population, as no data is available on the total number of Uro-oncologists and most specifically those dedicated to RCC. Although this figure is expected to be very high, a power calculation shows that the high response rate of our survey provided the sample with a 95\% of confidence (± 10\% of variability) and thus could be considered representative. The use of a convenience sample precludes extrapolation on the use of models and markers among general urologists not involved in oncology. The figures hereby presented might be even lower should general urologist have been surveyed. This is a further point of concern when considering the usefulness of more complex predictive models than the TNM.

With respect to the geographical distribution, as 70\% of the responders belonged to European countries, we cannot ensure that the results can be extrapolated to other continents. There were no apparent differences in response results between European and American urologists but the American sample was scarce.

CONCLUSIONS
The TNM staging system is universally used although only 40\% of the urologists acknowledge assessing prognostic in RCC. Preoperative prognostic models are scarcely used and postoperative models are only moderately used. There is no clear preference for any of the postoperative models. The main reasons that hinder the use of other prognostic models than the TNM are lack of accuracy, absence of additional benefit and lack of familiarity with. In metastatic setting the Motzer model is the most frequently used. Clinical, laboratory and pathological factors are being used by almost all urologists. Our data indicates that the penetration of the recently described staging models and integrated systems is at the most moderate, suggesting a limited use outside of the original developmental settings.

ACKNOWLEDGEMENTS
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REFERENCE LIST


27. Frank, I., Blute, M. L., Cheville, J. C. et al.: An outcome prediction model for patients with