Survival and Impact of Clinical Prognostic Factors in Surgically Treated Metastatic Renal Cell Carcinoma

Lorenzo Tosco, Hendrik Van Poppel, Bruno Freda, Giorgia Gregoraci, Steven Joniau

Article history:
Accepted September 14, 2012
Published online ahead of print on September 24, 2012

Keywords:
Metastatic renal cell carcinoma
Surgery
Cancer-specific survival
Prognosis

Abstract

Background: The survival impact of metastasectomy for metastatic renal cell carcinoma (mRCC) is still an active research field, particularly in the multimodal/targeted therapy era.

Objective: To determine the survival impact of clinical prognostic factors and their application to stratification of patients according to their prognosis so clinicians may be aided in their management of mRCC.

Design, setting, and participants: Retrospective, bi-institutional cohort study of 109 consecutive patients (71 male and 38 female; median age: 62 yr (range: 25–82 yr) with renal cell carcinoma (RCC) who underwent partial or radical nephrectomy and at least one metastasectomy for mRCC.

Intervention: Metastasis resection from various anatomic sites with the aim of completely removing detected lesions.

Outcome measurements and statistical analysis: Univariable and multivariable Cox regression models were used to analyse the impact of clinical prognostic factors on cancer-specific survival (CSS). Kaplan-Meier analysis with the log-rank test was used to compare CSS. Receiver operating characteristic (ROC) analysis was performed to test accuracy of prognostic groups. The α error for statistical significance was set at 0.05.

Results and limitations: Multivariable analysis revealed that primary tumour T stage ≥3 (hazard ratio [HR]: 2.8; p < 0.01), primary tumour Fuhrman grade ≥3 (HR: 2.3; p < 0.03), nonpulmonary metastases (HR: 3.1; p < 0.03), disease-free interval <12 mo (HR: 2.3; p < 0.058), and multiorgan metastases (HR: 2.5; p < 0.04) were independent pretreatment prognostic factors. Leuven-Udine (LU) prognostic groups based on these covariates were created and analysed with Kaplan-Meier and log-rank tests. The 2- and 5-yr CSS were significantly different; the respective group A CSS rates were 95.8% and 83.1%; group B, 89.9% and 56.4%; group C, 65.6% and 32.6%; and group D, 24.7% and 0% (p < 0.0001). ROC analysis on the accuracy of prognostic grouping revealed respective areas under the curve of 0.87 and 0.88 at 2 and 5 yr. Main limitations to present study are the retrospective design and the presence of different metastasis sites.

Conclusions: LU prognostic groups could be considered an accurate clinical tool to stratify patients according to prognosis and aid clinicians in the management of mRCC.

© 2012 European Association of Urology. Published by Elsevier B.V. All rights reserved.
1. Introduction

In 2008, 88,400 new diagnoses of kidney cancer and with 39,300 deaths from the disease were estimated in Europe [1]. Between 20% and 30% of patients have overt metastases at diagnosis [2] and 20% to 40% of patients progress to metastatic or locally recurrent disease after nephrectomy for localised disease [3]. Favourable trends in mortality from kidney cancer have been observed in recent years in Europe. However, the cause-effect relationship between these data and new trends in renal cell carcinoma (RCC) management is difficult to determine [4]. The role of surgery in the treatment of metastatic disease has been studied since 1939, the year of the first documented metastasectomy for metastatic RCC (mRCC) [5]. Kavolius et al. found a statistically significant difference in 5-yr overall survival (OS) of 44% versus 11% \( (p < 0.001) \), respectively, for patients treated with a surgical versus conservative approach [6]. Recent series have shown that patients undergoing liver metastasectomy had a higher 5-yr OS (62.2%) compared to a control group (29.3%; \( p = 0.003 \)) [7]. The 5-yr cancer-specific survival (CSS) rates for patients treated with complete multiple metastasis resections, incomplete resection, and conservative therapy were 49.4%, 23.7%, and 8.9%, respectively \( (p < 0.001) \) [8]. European Association of Urology guidelines suggest performing metastasectomy when lesions are resectable, even when synchronous [9], but the real impact of surgery, particularly in the multimodal management of mRCC, and the possible use of clinical prognostic factors should be confirmed in contemporary series.

The aim of this study was to analyse independent clinical predictors of survival to create clearly defined prognostic subgroups. We hypothesised that such subgrouping would facilitate an easy-to-use clinical model for survival prediction in patients affected by mRCC amenable to metastasectomy.

2. Materials and methods

After ethical committee authorisation, medical records of patients treated in two European university hospitals (University Hospitals Leuven [Leuven, Belgium] and University of Udine [Udine, Italy]) between 1988 and 2011 were reviewed. We analysed 132 consecutive patients who were treated at baseline with radical nephrectomy or partial nephrectomy and who underwent at least one metastasectomy for mRCC in different anatomic sites. We identified 109 patients for definitive analysis after eliminating subjects with incomplete data, with a presumed contralateral kidney metastasis, or with a diagnosis of a second cancer.

Surgical indication for nephron-sparing surgery was based mainly on tumour dimension, surgical feasibility, clinical absence of locally advanced disease, and presence of a solitary kidney (functional or anatomic). The following clinicopathologic variables were collected: sex, primary cancer characteristics (T stage, Fuhrman grade, histology); body mass index (BMI; kg/m\(^2\)) at time of nephrectomy, which was treated as categorical variable (underweight \( <18.5 \), normal \( 18.5 \sim \sim 25 \), overweight \( 25 \sim \sim 30 \), obese \( \geq 30 \)); age at metastasis outbreak; first-site metastasis details (site, synchronous, metachronous, disease-free interval [DFI], microscopic surgical margins at first metastasectomy); disease free interval (DFI, the period between the primary diagnosis of kidney cancer and the first metastasis outbreak); Eastern Cooperative Oncology Group (ECOG) performance status [10]; and cause of death. T stage was reassigned according to the 2009 TNM classification [11]; ECOG performance status was determined retrospectively at first metastasis outbreak. Synchronous lesions were considered as metastases diagnosed at the moment of primary nephrectomy.

Microscopic margins at metastasectomy were considered negative in all patients who had complete resections, and positive in all patients with tumour cells microscopically detectable at the inked edge of the specimen or with unavailable information on margins status (ie, margins not evaluable by the pathologist because of technical reasons, such as a fragmented resection specimen) (Table 1). Various anatomic sites were operated upon (Table 2).

None of the patients underwent immediate adjuvant systemic treatment and no patient received neoadjuvant drugs. Immunotherapy, cytokines, targeted therapy, and radiotherapy were only administered in case of inoperable/unresectable metastatic progression. Only patients who underwent at least one complete drug cycle were considered having received targeted therapy. Three (2.7%) patients abandoned treatment due to treatment-related complications.

Patients were followed up every six months. Abdominal and chest computed tomography scans were alternated with abdominal ultrasound and chest radiographs. Bone and brain scans were requested only in the case of overt symptoms. When new metastasis occurred, surgical resection was indicated in all cases when feasible. This was proposed not only in case of a solitary lesion, but also when multiple lesions in a single organ, or bilateral or multiple organs were involved. Subsequent metastasectomies were taken into consideration when complete resection was considered achievable. Survival was considered as the time from the first metastasectomy to the end of follow-up; CSS was the main endpoint of the study. Four (3.7%) patients died due to other causes, and were censored for the CSS endpoint. Leuven-Udine (LU) prognostic groups were conceived by combined premetastasectomy clinical features which were independent predictors of cancer-related death at multivariable analysis. Patients with increasing numbers of risk factors were plotted in separate groups using the Kaplan-Meier method to study the cumulative impact on CSS. Prognostic groups with overlapping survivals obtained on Kaplan-Meier analysis were combined into single groups.

Morbidity and mortality for metastasectomy was also studied: 124 metastasectomies (82.7%) were categorised according to the Clavien-Dindo classification of surgical complications [12,13].

CSS was calculated for all patients via Kaplan-Meier analysis and the log-rank test was used to compare survival among patient groups. Cox univariable analysis was performed and covariates with \( p < 0.2 \) were selected for multivariable analysis with the exception of clinically important issues that could be included for multivariable analysis even if not properly significant.

To estimate the accuracy of prognostic groups, a nonparametric receiver operating characteristic (ROC) analysis was performed for survival over 2 yr and 5 yr, with binomial estimation of confidence intervals (CI) of the area under the curve (AUC).

All significance levels were set at 0.05. MedCalc (MedCalc Software, Mariakerke, Belgium; and Stata/SE v.12.1 (StataCorp., College Station, TX, USA) were used for all statistical analyses.

3. Results

The study population comprised 109 patients (median age: 62 yr, range: 25–82 yr) treated primarily with nephrectomy and later with surgical resection of metastatic lesions. At baseline, 3 (2.7%) partial nephrectomies and 106 (97.3%) radical nephrectomies were performed. The median tumour diameter was 7.5 cm (range: 2–21 cm). At primary metastatic outbreak, 81 (74.3%) patients had metachronous...
lesions, 99 (90.8%) had lesions in a single organ, while 10 (9.2%) patients had multiorgan metastatic disease, involving adjacent organs in the majority of cases. Eleven patients underwent a maximum of three metastasectomies and two patients underwent four metastasis resections; the total number of metastasectomies was 150.

Clavien-Dindo classification of surgical complications was available for 124 metastasectomies. Median hospital stay was 9 d (range: 2–38), 55 patients (44%) did not have any classifiable complication, and 53 (43%) did not have need of intensive care support or other radiologic, endoscopic, or surgical interventions (Table 3).

Five-year CSS was 46.9% and median CSS was 54.7 mo (range: 0.4–211). The survival curves for various sites of metastasis at first relapse revealed a statistically significant \( p < 0.0001 \) difference between organ sites. The projected 5-yr CSS rates for metastasis at the following sites were: lung, 74%; splanchnic (liver, pancreas, contralateral kidney, adrenal, lymph nodes), 63%; uncommon sites (thyroid, parotid, skin, uterus, testis, gallbladder, pleura, ureter, breast), 30%; bone/vertebra, 27%; and multiorgan or brain, 0%. Twenty-eight (26%) patients underwent more than one metastatic resection and had a 5-yr CSS rate of 76% compared to 35% in patients who underwent a single resection \( (p = 0.005) \).

Median follow-up was 52.7 mo (range: 1.37–283 mo). At last follow-up, 46 (42.2%) patients had died from mRCC, 4 (3.7%) died from other causes, and 15 (13.8%) patients were lost to follow-up. Univariable (Table 4) and multivariable (Table 5) Cox regression analyses were also performed. Consecutive metastasectomies had a significant \( p = 0.008 \) positive impact on CSS (hazard ratio [HR]: 0.4; 95% CI, 0.16–0.75) at univariable analysis, but this issue was not included at multivariable analysis because only covariates related to the first metastasectomy were analysed.

BMI at nephrectomy time was studied at univariable analysis. BMI indicating overweight versus normal had an HR of 0.9 \( (p = 0.77; 95\% \text{ CI, 0.31–2.38}) \), HR for BMI obese versus normal was 0.2 \( (p = 0.16; 95\% \text{ CI, 0.03–1.78}) \), and there were no underweight patients of the 41 with available data.

At multivariable Cox regression, HR for targeted therapy was 0.6 \( (95\% \text{ CI, 0.28–1.44}) \), but it did not reach statistical significance \( p = 0.27 \). T stage, Fuhrman grade, DFI,
nonpulmonary lesions, and multiple lesions were independent predictors of survival (Table 5) and they were used to build LU prognostic groups (Fig. 1). We analysed CSS for each cumulative number of those risk factors using the Kaplan-Meier method with log-rank test. The corresponding 5-yr CSS rates were 80% (no risk factors), 81% (one risk factor), 60% (two risk factors), 32% (three risk factors), 0% (four and five risk factors) \( p < 0.0001 \). Because of overlapping survival, the groups with zero and one risk factor were considered as a single group (group A), as were the groups with four and five risk factors (group D). This simplified grouping model was reanalysed using Kaplan-Meier analysis with log-rank test; 2 and 5-yr CSS rates were 95.8% and 83.1%, 89.9 and 56.4%, 65.6% and 32.6%, and 24.7% and 0%, respectively, for groups A, B, C, and D \( p < 0.0001 \) (Fig. 2).

At ROC analysis, the AUC of our prognostic groups at 2-yr survival was 0.87 (95% binomial CI, 0.76–0.94), with the highest percentage of correctly classified subjects with four or more risk factors (80.88%). The AUC of our prognostic groups at 5-yr survival was 0.88 (95% binomial CI, 0.76–0.95), with the highest percentage of correctly classified subjects with two or more risk factors (84.21%).

### Table 3 – Clavien-Dindo classification of surgical complications

<table>
<thead>
<tr>
<th>Clavien-Dindo classification</th>
<th>Thoracic</th>
<th>Abdominal</th>
<th>Orthopaedic</th>
<th>Vertebral</th>
<th>Multiorgan</th>
<th>Other</th>
<th>Total</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>20</td>
<td>(16)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>18</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>33</td>
<td>(27)</td>
</tr>
<tr>
<td>3a</td>
<td>5</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>8</td>
<td>(7)</td>
</tr>
<tr>
<td>3b</td>
<td>2</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>(2)</td>
</tr>
<tr>
<td>4a</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>3</td>
<td>(2)</td>
</tr>
<tr>
<td>4b</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>None</td>
<td>17</td>
<td>14</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>13</td>
<td>55</td>
<td>(44)</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>43</td>
<td>11</td>
<td>7</td>
<td>9</td>
<td>15</td>
<td>124</td>
<td></td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; DFI = disease-free interval; BMI = body mass index.

### Table 4 – Univariable Cox regression analysis

<table>
<thead>
<tr>
<th>Covariates</th>
<th>HR</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T stage ≥3 vs &lt;3</td>
<td>3.7</td>
<td>0.0002</td>
<td>1.89–7.33</td>
</tr>
<tr>
<td>Fuhrman grade 3–4 vs 1–2</td>
<td>2.1</td>
<td>0.03</td>
<td>1.09–4.14</td>
</tr>
<tr>
<td>Sarcomatoid vs not sarcomatoid</td>
<td>2.3</td>
<td>0.16</td>
<td>0.72–7.46</td>
</tr>
<tr>
<td>Age, y, ≥70 vs &lt;70</td>
<td>1.1</td>
<td>0.79</td>
<td>0.53–2.28</td>
</tr>
<tr>
<td>ECOG PS ≥1 vs 0</td>
<td>2.1</td>
<td>0.02</td>
<td>1.14–3.77</td>
</tr>
<tr>
<td>DFI, mo: ≤12 vs &gt;12</td>
<td>2.6</td>
<td>0.002</td>
<td>1.43–4.74</td>
</tr>
<tr>
<td>Synchronous metastasis</td>
<td>2.8</td>
<td>0.0006</td>
<td>1.56–5.07</td>
</tr>
<tr>
<td>Nonpulmonary metastasis</td>
<td>4</td>
<td>0.004</td>
<td>1.58–10.1</td>
</tr>
<tr>
<td>Multiorgan metastasis</td>
<td>2.9</td>
<td>0.01</td>
<td>1.28–6.48</td>
</tr>
<tr>
<td>Resection margins</td>
<td>3.9</td>
<td>&lt;0.0001</td>
<td>2.15–7.04</td>
</tr>
<tr>
<td>Consecutive resections</td>
<td>0.4</td>
<td>0.008</td>
<td>0.16–0.75</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>0.72</td>
<td>0.38</td>
<td>0.35–1.50</td>
</tr>
<tr>
<td>BMI, kg/m²: overweight vs normal</td>
<td>0.9</td>
<td>0.77</td>
<td>0.31–2.38</td>
</tr>
<tr>
<td>BMI, kg/m²: obese vs normal</td>
<td>0.2</td>
<td>0.16</td>
<td>0.03–1.78</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; DFI = disease-free interval; BMI = body mass index.

### Table 5 – Multivariable Cox regression analysis

<table>
<thead>
<tr>
<th>Overall model fit: ( p &lt; 0.0001 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariates</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>T stage ≥3 vs &lt;3</td>
</tr>
<tr>
<td>Fuhrman grade ≥3</td>
</tr>
<tr>
<td>ECOG PS ≥1 vs 0</td>
</tr>
<tr>
<td>DFI, mo: ≤12 vs &gt;12</td>
</tr>
<tr>
<td>Nonpulmonary metastasis</td>
</tr>
<tr>
<td>Multiorgan metastasis</td>
</tr>
<tr>
<td>Targeted therapy</td>
</tr>
<tr>
<td>Synchronous metastasis</td>
</tr>
<tr>
<td>Sarcomatoid vs nonsarcomatoid</td>
</tr>
<tr>
<td>Resection margins</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; DFI = disease-free interval; BMI = body mass index.

Fig. 1 – Leuven-Udine prognostic groups.
4. Discussion

Various treatments have been proposed for mRCC. Surgery has demonstrated a positive impact in terms of survival even when complete resection is not possible [8,14]. Randomised clinical trials have shown that there is no effective immunotherapy for advanced RCC [15] and targeted therapies prolong progression-free survival more effectively than immunotherapy or placebo [16], with metastatic disease stabilisation even in >70% of patients [17–19] and the possibility of complete response [20]. Metastasectomy remains an important treatment for mRCC [21] and the growing evidence of long-term responses with targeted therapy has been stimulating multimodality approaches for this disease [22,23].

The concept of subsequent surgeries has been cited in some studies, but its real impact has to be clarified [6,14,24,25]. Kierney et al. did not detect statistically significant associations between any prognostic factor and the probability of having a second intervention; survival impact was not studied for patients with more than one metastasectomy [25]. Kavolius et al. retrospectively evaluated metastasectomy in 278 patients, including 110 who underwent subsequent interventions (two metastasectomies, 62 patients; three metastasectomies, 22 patients), but the 5-yr OS rate did not differ significantly from the group treated with a single intervention [6]. In our study, consecutive metastasectomies versus a single metastasectomy significantly correlated with improved CSS at univariable analysis (p = 0.008). However, it has to be stressed that only patients who were deemed good candidates for subsequent metastasis resection were selected for further surgery, while those who were not received palliative systemic treatments. Thus, the role of multiple surgeries as an independent predictor of survival was considered doubtful and not included in the multivariate analysis in this study.

BMI is a demonstrated independent prognostic factor for patients affected by RCC after nephrectomy [26]. At univariable analysis, overweight and obese patients had no influence on CSS in the present series. BMI was not included at multivariable analysis (1) to maintain the statistical power for the other covariates and (2) because BMI categories were not homogeneous.

Clinical and laboratory-based scores can predict survival after nephrectomy [27,28]; moreover, some recent studies have already provided prognostic scores in patients with pulmonary RCC metastases [29,30]. Development of standardised tools that help oncologists and surgeons assure the best therapeutic indication is still a challenge. The impact of five commonly available clinical risk factors (T stage [TNM 2009], Fuhrman grade at nephrectomy, DFI, multiple lesions, and extrapulmonary metastases) was further assessed using univariable and multivariable Cox regression models. All risk factors were confirmed to be independent predictors of survival in the present series. Further assessment using Kaplan-Meier analysis and the log-rank test allowed the creation of four demarcated prognostic subgroups (which we named Leuven–Udine prognostic groups), demonstrating that the more prognostic factors that are present, the higher the risk of dying from mRCC. The accuracy of our model was tested with ROC analysis and showed an overall good accuracy at 2 (AUC, 0.87) and 5 yr (AUC, 0.88). Thus, LU prognostic groups could be used to
stratify patients with mRCC at metastases outbreak, and if this tool was externally validated, it could become a clinical instrument to standardise therapy and compare data in future studies. The proposed LU prognostic groups have the advantage of providing CSS estimates for all patients affected by mRCC, not only for those with pulmonary metastases.

The present study has some limitations that are important to consider. The retrospective design and inclusion of different metastatic sites could incur bias probability. The prognostic impact of the microscopic margins at first metastasectomy should be confirmed in other series because of the possible impact of nonevaluable margins in the present study. BMI at time of nephrectomy was not successfully analysed mainly because of the retrospective nature of the study, but it would be useful to analyse it further to consider its role as a risk factor to improve the predictive value of LU prognostic groups. Another possible limitation is related to the ECOG performance status that was assigned retrospectively from patients’ files at first metastasis outbreak. The association of systemic treatments in addition to metastasectomy is a contemporary issue, but due to differences among drugs and schedules in our series, the real impact of the multimodal approach has not been completely defined.

5. Conclusions

Within the limits of present study, we can confirm the importance of a surgical approach to mRCC, also considering the low percentage of high-grade complications. Surgery should be indicated particularly for patients with resectable disease, good performance status, and predicted good CSS. From this point of view, LU prognostic groups could represent, if externally validated, an interesting tool to support clinicians in the treatment decision making for patients affected by mRCC.

**Author contributions:** Steven Joniau 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:** Joniau, Tosco.

**Acquisition of data:** Tosco, Joniau.

**Analysis and interpretation of data:** Tosco, Joniau.

**Drafting of the manuscript:** Tosco.

**Critical revision of the manuscript for important intellectual content:** Joniau, Tosco, Van Poppel, Freia.

**Statistical analysis:** Tosco, Gregoraci.

**Obtaining funding:** None.

**Administrative, technical, or material support:** None.

**Supervision:** Joniau, Van Poppel, Freia.

**Other (specify):** None.

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

**Funding/Support and role of the sponsor:** None.

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at [http://dx.doi.org/10.1016/j.eururo.2012.09.037](http://dx.doi.org/10.1016/j.eururo.2012.09.037).

**References**


