Kidney Cancer

Below Safety Limits, Every Unit of Glomerular Filtration Rate Counts: Assessing the Relationship Between Renal Function and Cancer-specific Mortality in Renal Cell Carcinoma

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Abstract

Background: The hypothesis that renal function could influence oncological outcomes is supported by anecdotal literature.

Objective: To determine whether estimated glomerular filtration rate (eGFR) is related to cancer-specific mortality (CSM) in patients who had undergone surgery for renal cell carcinoma (RCC).

Design, setting, and participants: A retrospective analysis of 3457 patients who underwent radical (39%) or partial nephrectomy (61%) for cT1–2 RCC between 1990 and 2015.

Outcome measurements and statistical analysis: The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. CSM was analyzed in a multivariable competing-risk framework, estimating the subdistribution hazard ratio (SHR) accounting for deaths from other causes. The relationship between eGFR and CSM was investigated from multiple statistical approaches—extended Cox regression with eGFR incorporated as a time-dependent covariate, landmark analysis, and joint modeling. Other predictors were selected by competing-risk random forest method and backward elimination.

Results and limitations: The relationship between eGFR and CSM was graphically described by a linear spline, i.e. a continuous piecewise linear function with two lines joined by a knot. For eGFR treated as a time-dependent covariate, the knot was located at 65 ml/min; at landmark analysis with eGFR at the baseline, 12 mo, and last functional follow-up, the knots were 85, 60, and 65 ml/min, respectively. In multivariable competing-risk analysis, CSM was associated with eGFR only for values of eGFR below these cutoffs, with SHRs for every 10 ml/min of reduction in eGFR of 1.25 (p = 0.003), 1.16 (p = 0.028), 1.44 (p = 0.02), and 1.16 (p = 0.042), corresponding to time-dependent eGFR, and eGFR at baseline, 12 mo, and last functional follow-up, respectively. Joint modeling confirmed these results. A retrospective design with inherent biases in data collection represents a limitation.

Conclusions: In patients undergoing surgery for RCC, renal function should be preserved in order to improve cancer-related survival.

Patient summary: The relationship between renal function and probability of dying due to renal cancer is complex. The present study found a correlation between glomerular filtration rate and cancer specific mortality that could reconsider the oncological role of renal function in patients undergoing surgery for renal cancer.

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1. Introduction

International guidelines [1,2] recommend partial over radical nephrectomy as the standard treatment for cT1 renal cell carcinoma (RCC) because of equivalent oncological outcomes [3] with superior preservation of renal function, postulated as beneficial to reduce cardiovascular mortality [4–6]. Thus, the indication to partial nephrectomy is progressively expanding even if the trade-off between advantages and surgical morbidity remains under debate [7].

The hypothesis that the amount of renal function could influence oncological outcomes is poorly intuitive and still neglected to date. However, at careful scrutiny within nephrology literature, it emerges that several large longitudinal population studies identified a linear inverse relationship between estimated glomerular filtration rate (eGFR) and cancer incidence or mortality [8–12].

If confirmed, this association would be paramount in surgical decision-making. The present study analyzed a large comprehensive dataset to investigate this hypothesis.

2. Patients and methods

Five academic tertiary institutions collected full data on patients who consecutively underwent surgery for cT1–2, N0, and M0 (AJCC/TNM 2017) RCC from 1990 to 2015.

Indication to partial nephrectomy was clinically organ-confined tumor deemed as technically resectable by an experienced surgeon at each institution. During the study period, the tumor size cutoff to attempt partial nephrectomy was progressively raised from 2–3 cm to 7 cm, in accordance with the contemporary guidelines [1,2].

The eGFR was evaluated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [13] at baseline, 12 mo after surgery, and last available follow-up, to account for complete stabilization from the surgical insult.

Patient’s life status was documented by planned controls, and causes of death were reported as related to RCC or due to other causes; incomplete information was supplemented by phone interviews or by consulting hospital and administrative registries.

2.1. Statistical analysis

The relationship between eGFR and cancer-specific mortality (CSM) was analyzed in a competing-risk framework [14], accounting for death from other causes. Subdistribution hazard ratio (SHR) is the ratio of the instantaneous risk at time t of having the event of death of two groups and can be interpreted as hazard ratios (HRs) of the Cox model. As readings were taken at three time points, two of which were fixed (baseline and 12 mo postoperatively) and the third one (last functional follow-up) scattered along the timeline, eGFR was first incorporated as a time-dependent covariate in an extended Fine and Gray model [15] by expanding data from one record per patient to one record per time interval per patient. The results of the model were compared with those of a landmark analysis [16] investigating the association between eGFR and CSM by setting three landmark time points (baseline, 12 mo, and last functional follow-up) and estimating a standard Fine and Gray model for each one with eGFR as a fixed-time covariate. Selection of predictors for all models was performed by estimating variable importance by the random survival forest method and then by backward elimination [17].

Exploratory graphs were drawn to visualize the relationship between eGFR and CSM: scatterplots with smoothed curves estimated by local regression (LOESS) suggested to model such a relationship by a linear spline, that is, a continuous piecewise linear function with two lines joined by a knot, the value of which was estimated by two different statistical methods [18,19]. Then, final competing-risk multivariable models were built taking into account the piecewise relationship.

As confirmatory analysis, the relationship between eGFR and CSM was investigated by the “joint modeling” [20] approach, which incorporated eGFR as a time-dependent covariate and accounted for the differences between pre- and postoperative periods by joining a linear mixed-effect model for longitudinal repeated measurements of eGFR and a Cox model with CSM as outcome, with a binary pre/post-covariate that differentiated between eGFR measurements before or after surgery.

A p value of <0.05 was considered statistically significant. Calculations were done with Stata 13 (StataCorp, College Station, TX, USA) and R (version 3.4.4; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The dataset included 3457 patients with cT1a/T1b/T2, N0, M0 RCC; 1335 (39%) underwent radical nephrectomy and 2122 (61%) partial nephrectomy (Table 1).

Median functional follow-up was 61 mo (interquartile range [IQR] 24–118) with 7381 eGFR assessments recorded (2939 at baseline and 4442 after a minimum of 12 mo from surgery); 40%, 35%, and 26% of patients had three, two, and one measurement, respectively; 66% had both pre- and postoperative measurements, 19% the preoperative one only, and 14% the postoperative one only. Median eGFR was 78.5 (IQR 65.4–92.6) ml/min at baseline, 71.4 (IQR 54.6–89.6) ml/min after 12 mo, and 64.4 (IQR 51.5–79.3) ml/min at the last functional follow-up; the respective percentages of patients at chronic kidney disease (CKD) stage ≥3 were 16%, 33%, and 38%.

Overall 3008 patients were alive without evidence of recurrence (follow-up >60 mo in 48%); 128 died due to RCC and 278 due to other causes. The estimated overall survival rates at 60 and 120 mo were 93% and 84%, respectively.

Table 2 reports competing-risk univariate analysis: CSM was found to be significantly associated with age, gender, and descriptive tumor features (staging, grading, clear cell histology, and necrosis). Notably, eGFR and the presence of stage 3 CKD were found to be significantly related to CSM, with SHRs of 0.70 and 1.95, respectively.

The relationship between the CSM and eGFR based on all, baseline, 12-mo, and last available functional data—adjusted for gender, age, pT stage, grading, and type of surgery—was graphically investigated as exemplified by Figs. 1 and 2, referring to the analysis of the whole data with eGFR as time dependent. As anticipated, this preliminary evaluation was suggested to model the relationship by a continuous piecewiselinear function in which two lines are joined by a knot. The two statistical methods applied for knot location [18,19] were consistent in finding a cutoff of 65 ml/min with eGFR as a time-dependent covariate, and 85, 60, and 65 ml/min with eGFR as a time-fixed covariate at baseline, 12 mo, and last functional follow-up, respectively.
The analysis was replicated by splitting the cohort according to the type of surgery: breakpoints at 65 ml/min were estimated for both the subgroups, and a linear and inverse relationship between eGFR and CSM was found only below this value (partial nephrectomy SHR 1.35 [95% CI 1.02–1.92, p = 0.038]; radical nephrectomy SHR 1.23 [95% CI 1.03–1.47, p = 0.026]).

4. Discussion

The main finding of the present study was that renal function showed an independent relationship with CSM, after accounting for other strong prognostic factors and competitive causes of mortality. This relationship was modeled by a “piecewise” linear function with a cutoff of 65 ml/min considering all data, 85 ml/min for preoperative values only, and between 60 and 65 ml/min for postoperative values only. It is likely that renal function becomes a determinant of CSM only when a certain degree of impairment is exceeded, according to a “threshold effect.” In other words, the amount of renal detriment due to renal failure becomes a determinant of CSM only when a certain threshold of renal function is exceeded, according to a “threshold effect.” In other words, the amount of renal function over breakou...
These results could influence surgical indication: as such, patients with baseline eGFR below 85 ml/min would start within the “risk” zone where any decrease of renal function would proportionally worsen CSM, unless postoperative eGFR was maintained over 60–65 ml/min. Accordingly, partial nephrectomy should be preferred. Conversely, in patients for whom postoperative eGFR could be secured above 60–65 ml/min, the role of surgery seems to be less determinant and they can be good candidates for radical nephrectomy as well. However, caution is needed considering that the prognostic relevance of preoperative eGFR raises the possibility that existing comorbidities could be equally or even more determinant than surgically induced CKD.
Large population [21] and retrospective hospital studies [3–5,22] reported that renal function plays an independent role on non–cancer-related mortality. Definitely, the relationship between renal function and non–cancer-related mortality is robust and widely accepted, as also confirmed in our dataset by a multivariable Cox regression after accounting for several patient- and tumor-related confounders (HR for eGFR 0.98, 95% CI 0.98–0.99, p < 0.001; analysis not reported).

Conversely, at present, the urological community has omitted the hypothesis that the impairment of renal function could impact CSM, although there is evidence that CKD, also at an initial stage, may worsen the response against cancer. Indeed, large longitudinal population studies showed a linear inverse relationship between eGFR, incidence of cancer [7–11], and CSM [10,23,24], in particular for RCC. Mok et al [23] reported a linear inverse relationship between eGFR <45 ml/min and CSM, especially for RCC, in 367 392 patients followed for a median of 9.8 yr. Iff et al [24] found a linear inverse relationship between eGFR <60 ml/min and CSM in 4077 patients followed for a median of 12.8 yr; this relationship was more robust for breast and urinary cancers and independent of competing causes of mortality. Weng et al [10] found an increased risk of CSM proportional to eGFR reduction in 123 717 Taiwanese followed for a median of 7 yr; again, this effect was more pronounced for liver, kidney, and urinary tract cancers. In addition, one retrospective multi-institutional “urological” paper reported worse CSM after radical nephrectomy in 200 patients with preoperative CKD when compared with 600 matched controls [25].

With respect to the existing literature, the present study provides detailed information on treatments and pathological features, major determinants of CSM crucial to adequately conduct survival analysis. Renal function was longitudinally recorded during follow-up, and not only at baseline, in order to investigate whether CSM had a relationship with synchronous eGFR. Finally, statistical methods and prolonged follow-up allowed for the adjustment of the association between renal function and CSM for competitive causes of mortality, especially relevant in such population with low-risk renal cancer.

Table 3 – Multivariable regression Fine and Gray extended model to estimate the relationship with cancer-specific mortality accounting for competing risks in pre- and postoperative periods

<table>
<thead>
<tr>
<th>Feature</th>
<th>SHR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female vs male)</td>
<td>0.57</td>
<td>0.37–0.87</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (yr, continuous)</td>
<td>1.01</td>
<td>0.99–1.03</td>
<td>0.27</td>
</tr>
<tr>
<td>Type of surgery (radical vs partial nephrectomy)</td>
<td>2.43</td>
<td>1.35–4.37</td>
<td>0.003</td>
</tr>
<tr>
<td>pT (T1b vs T1a)</td>
<td>1.86</td>
<td>1.07–3.24</td>
<td>0.03</td>
</tr>
<tr>
<td>pT (T2 vs T1a)</td>
<td>2.92</td>
<td>1.57–5.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pT (T3–T4 vs T1a)</td>
<td>3.89</td>
<td>2.16–7.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grading (high vs low)</td>
<td>1.67</td>
<td>1.10–2.61</td>
<td>0.015</td>
</tr>
<tr>
<td>eGFR below breakpoint (continuous, intervals of 10 ml/min)</td>
<td>1.25</td>
<td>1.07–1.44</td>
<td>0.003</td>
</tr>
<tr>
<td>eGFR above breakpoint (continuous, intervals of 10 ml/min)</td>
<td>1.04</td>
<td>0.86–1.26</td>
<td>0.72</td>
</tr>
</tbody>
</table>

The eGFR was incorporated as a time-fixed and time-dependent covariate in pre- and postoperative models, respectively. Breakpoint was at 65 ml/min. CI = confidence interval; eGFR = estimated glomerular filtration rate; SHR = subdistribution hazard ratio.

Comprehensive meta-analysis of retrospective observational studies showed that partial nephrectomy had lower CSM than radical nephrectomy, providing a 29% risk reduction in CSM (HR 0.71, p < 0.001) [3] despite comparable tumor characteristics. Such a paradoxical association between most radical therapies and the worse oncological outcome was also found in our results, but no causality should be claimed since selection bias was not controlled due to the retrospective design of studies. Nevertheless, we attempted to mitigate this bias during the assessment of the eGFR/CSM relationship, including several tumor-related features in multivariable analyses, and also of the type of surgery per se. Further subgroup analysis confirmed our findings in patients submitted to partial or radical nephrectomy only. Ultimately, it seems that the relationship between eGFR and CSM was not influenced by tumor-related features, explicitly reported or hidden behind the type of surgery.

Our findings pose some concerns regarding the results of previous retrospective studies comparing the oncological outcomes of partial versus radical nephrectomy, neglecting the role of renal function as a prognostic factor. The hypothesis that higher preservation of renal function could have impacted these results, by favoring the patients who underwent partial nephrectomy due to superior preservation of renal function, should be discussed. In opposition to these considerations, the randomized trial EORTC 30904 [26,27] reported comparable CSM after partial and radical nephrectomy. Besides the numerous limitations of this trial [28], it should be remarked that oncological and functional follow-up periods were not congruent (median time 9.3 vs 6.7 yr) and that the analyses were not adjusted for competing causes of mortality, despite a large number of patients dying from non–cancer-related causes.

We acknowledge that the association of renal function with prognosis after cancer surgery is not intuitive and that the underlying causes are difficult to deduce. Nevertheless, in patients with decreased renal function, there is a complex set of disorders of the adaptive immune system that has been investigated in depth. Loss of renal function determines the onset of a vicious loop in which the immune system is both activated in a proinflammatory direction and suppressed, finally leading to uremia-related immune...
deficiency [29]. More extensively, CKD causes a preferential loss of number and function of lymphoid cells through the loss of thymic function, attrition of telomeres, and expanded memory T-cell population, which was compatible with the concept of premature immunological aging on the whole [30]. Finally, it could be hypothesized that preservation of renal function promotes physical and mental health status, and contributes to improving the host’s defense against cancer.

The present study was not devoid of limitations. The first was the retrospective design with inherent biases in data collection, particularly concerning the proteinuria (the lack of this information compromised a more accurate estimation of renal damage) and the pattern of missing eGFR measurements. Second, as only cT1/2 renal masses were included as cases amenable for both partial and radical nephrectomy, for more advanced tumors the association eGFR/CSM might be masked by the prevailing role of pathological adverse features. Third, it cannot be excluded that functional impairment could be related to CSM just because a proxy of tumor volume and complexity, but due to the lack of a radiological review this issue cannot be addressed. Fourth, the long time span of the study impacted the surgical technique, with a shift toward minimally invasive approaches. Finally, we claim that the length of follow-up could be inadequate to clearly depict CSM in a cohort of patients mainly affected by low-risk tumors, burdened by a 5% risk of “very late” (>10 yr) recurrences [31].

5. Conclusions

The relationship found between eGFR and CSM indicates that renal function could have an oncological role in patients undergoing surgery for RCC. Whenever feasible, nephron-sparing approaches should be preferred, unless extirpative surgery could equally warrant the preservation of renal function above specific limits.

Author contributions: Alessandro Antonelli 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: Antonelli, Minervini, Capitanio.

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Analysis and interpretation of data: Antonelli, Sandri.

Drafting of the manuscript: Antonelli.

Critical revision of the manuscript for important intellectual content: Terrone, Romagnani, Minervini, Capitanio, Mari, Bertolo.

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Other: None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.07.029.

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