Published in final edited form as:

Urol Oncol. 2015 September ; 33(9): 388.e19–388.e25. doi:10.1016/j.urolonc.2014.06.004.

Lymphopenia is an Independent Predictor of Inferior Outcome in Papillary Renal Cell Carcinoma

Reza Mehrazin¹, Robert G. Uzzo¹, Alexander Kutikov¹, Karen Ruth², Jeffrey J. Tomaszewski¹, Essel Dulaimi³, Serge Ginzberg¹, Philip H. Abbosh¹, Timothy Ito¹, Anthony T. Corcoran¹, David Y. T. Chen¹, Marc C. Smaldone¹, and Tahseen Al-Saleem³

¹Division of Urologic Oncology, Fox Chase Cancer Center-Temple Health System, Philadelphia, PA, 19111

²Division of Biostatistics, Fox Chase Cancer Center-Temple Health System, Philadelphia, PA, 19111

³Division of Pathology, Fox Chase Cancer Center-Temple Health System, Philadelphia, PA, 19111

Abstract

Purpose—Lymphopenia as a likely index of poor systemic immunity is an independent predictor of inferior outcome in clear renal cell carcinoma (ccRCC). We sought to evaluate the prognostic relevance of preoperative absolute lymphocyte count (ALC) in a cohort of papillary renal cell carcinoma (PRCC) patients.

Materials & Methods—A prospectively maintained, renal cancer database was analyzed. Patients with preoperative ALC, within 3 months prior to surgery, were eligible for the study. Those with multifocal or bilateral renal tumors were excluded. Correlations between ALC and age, gender, smoking, Charlson comorbidity index (CCI), pathologic (pT) stage, PRCC subtype, and TNM stage were evaluated. Differences in overall survival (OS) & cancer-specific survival (CSS) by ALC status were assessed using the log-rank test and cumulative incident estimators, respectively. Cox proportional hazards modeling was used for multivariable analyses (MVA).

Results—192 patients met the inclusion criteria. As a continuous variable, preoperative ALC was associated with higher TNM stage ($p=0.001$) and older age ($p=0.01$). As a dichotomous variable, lymphopenia ($<1,300$ cells/ μ l) was associated with higher TNM stage ($p=0.003$). On MVA, controlling for covariates, after a median follow up of 37.3 months, lymphopenia was associated with inferior OS (HR=2.3 [95%CI 1.2–4.3], $p=0.011$) and trended to significance for CSS ($p=0.071$). Among non-metastatic, lymphopenic patients, OS at 37.5 months was shorter compared to those with normal ALC (83% vs. 93%, $p=0.0006$).

Correspondence Author: Tahseen Al-Saleem, M.D., Department of Pathology, Fox Chase Cancer Center, 333 Cottman Ave, Philadelphia, PA, 19103. Tel: 215-728-3850, Fax: 215-728-2848, T_Alsaleem@fccc.edu.

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

Conclusions—In patients with PRCC, lymphopenia is associated with lower survival independent of TNM stage, age, and histology. ALC may provide an additional pre-operative prognostic factor.

Keywords

Renal cell carcinoma; Papillary Renal Cell Carcinoma; Lymphopenia; Inflammatory Disease; Biomarker; Survival; Lymphocyte Count

Introduction

Kidney cancer, predominantly renal cell carcinoma (RCC), is among the most lethal of urologic malignancies and in 2014, in the United States, 63,920 new cases are estimated, with approximately 22% rate of cancer-specific mortality.¹ Although 20-30% of patients can experience relapse within the first 3 years, surveillance is the standard of care after the curative-intent surgery for localized or locally advanced RCC.² Existing preoperative RCC models that risk-stratify patients are useful guides after surgery but are of limited value in a preoperative setting. To estimate the risk of disease recurrence for localized RCC, only a limited number of models and nomograms based on TNM stage, nuclear grade, tumor necrosis, microvascular invasion, and performance status have been proposed.²⁻⁶ Moreover, the most commonly used prognostic factor models for RCC are derived from the era of immunotherapy and are limited to a population of patients with advanced RCC.^{7, 8}

Over the last several years prognostic systemic inflammatory markers such as, erythrocyte sedimentation rate (ESR)⁹, platelet count¹⁰, C-reactive protein (CRP)¹¹, vascular endothelial growth factors (VEGF)¹², and serum interleukin-6 levels (IL-6)¹³, related to RCC outcomes have been described. More recently, there has been an increased interest in evaluating the host's inflammatory and immune response to tumors. One routinely obtained and readily available marker of the systemic inflammatory response is the absolute lymphocyte count (ALC), and its preoperative prognostic value as an independent predictor of disease free survival (DFS) and all-cause overall survival (OS) in clear RCC has been previously described by our group.¹⁴

Papillary RCC (PRCC) is the second most common histologic subtype of RCC which originates from a different biological pathway and along with clear cell histology, they make up majority of RCC cases seen in clinical settings.¹⁵ To our knowledge, the role of ALC as a biomarker has not yet been fully evaluated as a predictor of survival in patients with PRCC. The aim of our study was to evaluate the prognostic significance of preoperative ALC in our large uniform PRCC series, as our group has done for clear cell RCC (ccRCC) before.¹⁴ We hypothesized that preoperative ALC may be a significant predictor of PRCC outcome as well. If preoperative ALC is indeed a significant predictor of outcome in PRCC, and since ccRCC and PRCC constitute the vast majority of RCC's, then ALC can be used as a useful preoperative predictor of RCC outcome even if the histology is not known yet.

Material and Methods

The institutional, prospectively-maintained, renal tumor database at Fox Chase Cancer Center was used to identify patients with PRCC, who underwent surgery from 2000 to 2013. Patients who did not have ALC value within 3 months preoperatively were excluded from analysis. Since the outcome could have been affected by another primary rather than the PRCC index tumor, those patients who had more than one surgery for management of multifocal or bilateral renal tumors were also excluded. Age at the time of surgery, gender, clinical and pathological parameters, Charlson comorbidity index (CCI), and history of smoking were considered as potential confounders.¹⁴

Renal tumors were managed and surgically treated as previously described.¹⁶ Most nephrectomy specimens were examined and graded by two urooncological pathologist (TAS and EDA). Immunohistochemical stains and cytogenetics were used as adjuncts, as necessary. Type I and II PRCCs were identified mainly by their nucleolar features; either absent (or very small) or prominent/pleomorphic nucleoli, respectively. Generally, type I is considered as “low grade,” type II as “high grade,” and the sarcomatoid PRCC classified as such.¹⁷ TNM staging was determined using a collaborative stage approach, combining pathological and clinical findings from patient records, the tumor registry, and the kidney cancer database. Pathologic T (pT) stage was designated pathologically and M stage was assigned mostly clinically (based on cross sectional imaging). If lymphadenectomy was not performed at the time of surgery, N stage was assigned clinically. Collaborative staging was revised according to the cancer staging manual of the American Joint Committee on Cancer, 7th edition.¹⁸ The postoperative surveillance was physician-dependent, often using the recommended follow-up (www.cancernomograms.com).

At our tertiary care cancer center, lymphopenia is defined as ALC of 1,300 cells/ μ l or less. We examined ALC both as a continuous and a dichotomous variable. One-way ANOVA or t-tests were used to assess differences in mean ALC levels, and trends were evaluated using linear regression with the assumption of equal spacing between stage levels. Fisher's exact test was used to assess for differences in stage and PRCC type by low ALC, and the Cochran-Armitage test for trends.

The association between lymphopenia and mortality in PRCC patients was examined. OS was estimated using Kaplan-Meier methods, and differences by lymphopenia status were assessed by the log rank test. CSS was estimated using cumulative incident estimators to account for the competing risk of other causes of death. Differences in CSS by lymphopenia status were assessed using Fine and Gray's competing risk regression. As part of the prospective maintenance of the database, date and cause of death were obtained from the death certificate, patient's family, or local physician. Length of follow-up was calculated from the date of surgery to the date of last follow-up or death. OS and CSS were calculated from the date of surgery to the date of death from any cause and date of patients' cancer-related death, respectively. Cox proportional hazards regression was used for inferences about the relationship of overall mortality with low ALC and potential confounders. Potential confounders were consistent with our analysis of ccRCC cohort: age at surgery (<60 vs. 60 years, (closest round figure to the median)), CCI (<2 vs. 2), pT stage

(pT1p/T2 vs. pT3/pT4), N stage (N0 vs. N1), M stage (M0 vs. M1), PRCC type (I vs. II), and smoking history (ever vs. never).¹⁴ In order to determine the impact of low ALC on mortality, covariates which were associated with overall and PRCC related mortality on univariate analysis were included in the multivariable models. All statistical testing was two-sided, with significance defined as $p < 0.05$. Analyses were done using Stata software (version 12.1, StataCorp, College Station, TX) and SAS/STAT software (Cary, NC), version 9.3.

Results

Patient Characteristics

Out of 293 patients with a pathologic diagnosis of PRCC, 101 were excluded; 44 due to multiple surgeries for either bilateral or multifocal tumors, 55 due to absence of ALC on record, and two because of high ALC considered suspicious for chronic lymphocytic leukemia. Except for slightly lower nuclear tumor grade in the excluded cases, all tumor and patients' characteristics were not statistically different between the exclusion and the final cohorts. 192 patients met the inclusion criteria, of which 143 (74.5%) were males. The median age for the entire cohort was 61.5 years (mean, 62.0; range, 35-89), with the median CCI of 1.7 (mean, 1.7; range, 0-11). Median ALC was 1,600 cells/ μ l (mean 1.6; range, 0.5-3.5; figure 1a) and the median interval from its measurement to surgery was 11 days (mean, 12.9; range, 1-54). Within the median follow-up of 37.3 months (mean, 38.7; range 0.3-129.3) there were total of 42 deaths, of which 24 (57%) attributed to PRCC. The median Nephrometry Score for all of the renal tumors within the cohort was 8a (mean, 7.50; range, 4-12). One hundred twenty one (63%) patients had nephron sparing surgery (NSS), while 71(37%) underwent RN. Among those who had a NSS, 71 were treated with a minimally invasive approach (59 robotic-assisted and 12 laparoscopic PN) and 49 had open PN. Pathologic nodal evaluation, by lymphadenectomy, was available on 28% of the patients and clinical nodal evaluation was available for the remainder of the cohort.

Correlation of ALC with known prognostic factors—Correlation between ALC and patient characteristics is summarized in Table 1. As a continuous variable, lower ALC correlated with higher pT stage ($p=0.01$), overall TNM stage ($p=0.01$), CCI 2 ($p=0.017$), age ≥ 60 years ($p=0.01$), and male gender ($p=0.04$). Of other host related factors, higher ALC was also associated with history of smoking ($p=0.05$). As a dichotomous variable, lymphopenia ($<1,300$ cells/ μ l) was associated with higher pT stage ($p=0.002$), TNM stage ($p=0.005$), and CCI 2 ($p=0.004$).

Overall survival and cancer-specific survival—To investigate whether the ALC was associated with the clinical outcome of PRCC patients, univariable and multivariable analyses for the two end points were performed (Tables 2 & 3). Survival was examined in the subset of patients ($n=176$) who had a minimum of 12 months of follow-up (92% of the cohort). In this subset of patients, the median follow-up was 35.7 months and lymphopenia was found to be associated with lower all-cause OS (Figure 1b) and CSS (Figure 1d). On UVA, lymphopenia, advanced TNM stage, and PRCC type II were associated with inferior OS ($p=0.004$) and CSS ($p=0.038$). On MVA, with adjustment for these covariates,

lymphopenia was found to be statistically a significant independent predictor of inferior OS (HR= 2.28 [95%CI 1.21–4.28], $p=0.011$), (Table 2), In addition, it showed a strong trend toward significance for inferior CSS ($p=0.071$), which may be due to the relatively small number of cancer-related deaths (Table 3). Interestingly, the only other predictor of OS was the TNM stage; and for CSS TNM stage and PRCC subtype were the two other predictors.

In a separate Cox model, ALC as a continuous variable, was significantly associated with overall mortality (HR=0.36, [95%CI 0.19-0.68], $p=0.0018$). The association between low ALC and OS for localized disease at surgery (stages I and II) was examined separately, and lymphopenia was also found to be a significant predictor of OS in low stages ($p=0.050$). Since metastatic RCC can have a different biology, we analyzed OS among non-metastatic (M0) patients and lymphopenia was found to be a significant predictor of inferior OS in these patients as well ($p<0.001$, figure 1c). Thirty-six-month survival analysis showed significant survival advantage in patients with localized and locally advanced disease (M0), who had normal ALC compared to those with $ALC<1,300$ cells/ μ l prior to surgery (92.8% vs. 82.9%, $p<0.001$). As expected, patients with metastatic disease had inferior OS and CSS survival when analyzed separately ($p=0.001$ for both), tables 2 and 3.

We examined other possible confounding factors that could affect ALC and/or OS. Even though, current and former smokers had significantly higher ALC than nonsmokers, regardless of stage, smoking was found to be of borderline significance for OS ($p=0.053$). Twenty six patients had diabetes mellitus; but diabetic status was also not correlated with OS ($p=0.57$). Hypothyroidism (8 patients), chronic kidney disease (9 patients), sarcoidosis (1 patient), lupus (1 patient), and rheumatoid arthritis (2 patients) were not associated with lower ALC as well. Moreover, the medication profile of each patient was evaluated for medicines which could affect ALC; other than various nonsteroidal anti-inflammatory drugs and steroids (14 patients), none of the patients used immunomodulatory drugs, such as methotrexate, tacrolimus, sunitinib, or sorafenib (Table 4).

Discussion

To our knowledge, this is the first study, evaluating the role of preoperative ALC as a prognostic factor in PRCC tumors. Our current analysis, of a large and uniform cohort, suggests that preoperative ALC can be an important independent prognosticator of clinical outcomes and survival in patients with PRCC. On MVA, lymphopenia was found to be a strong predictor of inferior all-cause mortality (OS) along with advanced TNM stage.

Although several novel molecular changes in RCC have been identified, clinical TNM stage and pathological information, if available by core needle biopsy, continue to be used as the most common pre-operative predictive tools for survival and for patient counseling. Even though prognostic nomograms have been introduced to aid clinicians, most of them are constructed based on clear cell histology subtype and are less useful for prediction of survival in patients with PRCC. Generally, prognosis of patients with PRCC is known to be better than those with ccRCC, however, some of them, especially those with PRCC type II, can show early recurrence and die of metastatic disease.¹⁹ Lower incidence and heterogeneity of PRCC has made identification of prognostic features further challenging for

this disease. Although stage, nucleolar grade, tumor size, and coagulative tumor necrosis have been shown as prognostic factors in PRCC^{6, 19, 20}, to our knowledge, the role of ALC in predicting survival for this disease entity has never been reported.

Even though the link between cancer and inflammation was first described by Virchow in the mid-19th century,²¹ the mechanism which links biology of the host with tumor still remains unexplained. Over the last decade, there has been increasing evidence that cancer-related inflammation is a major determinant of outcome in cancer patients. The systemic inflammation initiated by tumors known to cause apoptosis and/or margination of the white blood cells leading to a drop in lymphocytes,²² and perhaps this tumor-associated immune dampening is one of the reasons for poor survival in cancer patients. Specifically, in RCC, studies have shown the anti-tumorigenic effect of lymphocyte infiltration (lymphocytosis) and favorable clinical outcomes in patients in whom high levels of lymphocytic attractant chemokines were detected.^{23, 24}

Lymphopenia and rise in absolute neutrophil count (ANC) are known indicators of proinflammatory response, which correlate with poor cancer survival. Previously, we have shown that preoperative lymphopenia is associated with inferior outcome in ccRCC.¹⁴ Others have shown an increase in NLR in non-metastatic^{25, 26} and metastatic^{24, 27, 28} ccRCC are associated with poor OS. Moreover, in a cohort of “non-clear cell” RCC, an increase in NLR, was shown to be independently associated with DFS.²⁸ Even though this was a multi-institutional study, some possible confounding factors that could influence the NLR and lymphocyte count, such as smoking, uremia, autoimmune or inflammatory diseases, were not addressed in the analysis.

Although some studies have shown rise in NLR as a poor prognostic factor for RCC and various other cancers^{25-27, 29} others have not been able to reproduce similar results.^{26, 30} In studies by Santoni et al.²⁷ and Ohno et al.,^{25, 29} although they reported NLR as a significant predictor of poor outcome in clear RCC, on MVA, ANC was not an independent prognostic factor for PFS and OS. In addition, in a prospective cohort study of localized RCC by Ramsey and colleagues,¹¹ neutrophilia was also not associated with cancer and disease specific survival. With the exception of few studies which NLR was evaluated as a continuous variable,^{28, 30} other prior reports, categorized it either based on the optimal statistical outcome or institutional laboratory cutoffs.^{11, 20, 25-27, 29} For statistical analysis, consistent with our prior report in clear RCC,¹⁴ rather than two opposing parameters, we tested the effect of a single parameter separately and on both UVA and MVA, lymphopenia was strongly correlated with inferior outcomes. We also examined the effect of ALC on outcome as a continuous variable rather than our own institutional cut-off alone.

As is the case in any retrospective study, there are some inherent limitations to our study, such as data selection and analysis which are susceptible to biases. To conduct a study on a homogenous population, we excluded patients with non-papillary histology, hereditary RCC, and those with cancers originating from other sites. Although we controlled for variables that can influence the ALC level (medications, medical comorbidities, inflammatory diseases, smoking), ALC could have been affected by non-captured subclinical infection or other neoplasm. Moreover, ALC was not compared to other known

RCC inflammatory prognostic factors (ESR, CRP, VEGF, serum IL-6); as they are not routinely part of our institution's preoperative laboratory work-up. As in other biological parameters, there are inherent variabilities in ALC estimations depending on the patient's age, gender, time between the test and surgery, and even the time of day that the test was performed.

Despite the limitations, our study suggests that pre-treatment ALC is associated with OS and may be introduced into clinical practice. Biomarkers have been targeted to best achieve the elusive goal of matching intensity of treatment to the patient and his/hers individual tumor biology. Current body of evidence suggests that ALC may serve as a useful adjunct to already established PRCC prognosticators^{6, 19, 20} to help identify patients with clinically significant disease, who may benefit from enrollment into neoadjuvant or adjuvant clinical trials, and provide cues to tailor individual patient post-operative surveillance schedules. This may be true not only for RCC, but for other cancers and lymphomas. Larger cohorts (multi-institutional) on the role of this biomarker in PRCC are necessary to validate our results.

Conclusions

Similar to our cohort of ccRCC, in patients with PRCC, lymphopenia was associated with lower OS independent of TNM stage, age, PRCC subtype, and CCI. ALC may contribute to already established prognostic factors and can be helpful for patient counseling. It may enhance the development of specific immunomodulatory approaches or design of clinical trials for management of patients with RCC.

Acknowledgments

The authors would like to thank Debra Kister and Michelle Collins for their management of the Fox Chase Kidney Cancer Keystone Database

This publication was supported in part by grant number P30 CA006927 from the National Cancer Institute. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. Additional funds were provided by Fox Chase Cancer via institutional support of the Kidney Cancer Keystone Program.

References

1. Siegel R, Ma JM, Zou ZH, et al. Cancer Statistics, 2014. *Ca-a Cancer Journal for Clinicians*. 2014; 64:9. [PubMed: 24399786]
2. Eggener SE, Yossepowitch O, Pettus JA, et al. Renal cell carcinoma recurrence after nephrectomy for localized disease: predicting survival from time of recurrence. *J Clin Oncol*. 2006; 24:3101. [PubMed: 16809736]
3. Cindolo L, Chiodini P, Brookman-May S, et al. Assessing the accuracy and generalizability of the preoperative and postoperative Karakiewicz nomograms for renal cell carcinoma: results from a multicentre European and US study. *BJU Int*. 2013; 112:578. [PubMed: 23470199]
4. Kutikov A, Egleston BL, Wong YN, et al. Evaluating overall survival and competing risks of death in patients with localized renal cell carcinoma using a comprehensive nomogram. *J Clin Oncol*. 2010; 28:311. [PubMed: 19933918]
5. Meskawi M, Sun M, Trinh QD, et al. A review of integrated staging systems for renal cell carcinoma. *Eur Urol*. 2012; 62:303. [PubMed: 22575911]

6. Klatte T, Remzi M, Zigeuner RE, et al. Development and external validation of a nomogram predicting disease specific survival after nephrectomy for papillary renal cell carcinoma. *J Urol.* 2010; 184:53. [PubMed: 20478577]
7. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol.* 2002; 20:289. [PubMed: 11773181]
8. 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. [PubMed: 19826129]
9. Magera JS Jr, Leibovich BC, Lohse CM, et al. Association of abnormal preoperative laboratory values with survival after radical nephrectomy for clinically confined clear cell renal cell carcinoma. *Urology.* 2008; 71:278. [PubMed: 18308103]
10. Gogos C, Baltaci S, Filiz E, et al. Significance of thrombocytosis for determining prognosis in patients with localized renal cell carcinoma. *Urology.* 2004; 63:447. [PubMed: 15028435]
11. Ramsey S, Lamb GW, Aitchison M, et al. Prospective study of the relationship between the systemic inflammatory response, prognostic scoring systems and relapse-free and cancer-specific survival in patients undergoing potentially curative resection for renal cancer. *BJU Int.* 2008; 101:959. [PubMed: 18190639]
12. Scartozzi M, Bianconi M, Faloppi L, et al. VEGF and VEGFR polymorphisms affect clinical outcome in advanced renal cell carcinoma patients receiving first-line sunitinib. *Br J Cancer.* 2013; 108:1126. [PubMed: 23511629]
13. Negrier S, Perol D, Menetrier-Caux C, et al. Interleukin-6, interleukin-10, and vascular endothelial growth factor in metastatic renal cell carcinoma: prognostic value of interleukin-6--from the Groupe Francais d'Immunotherapie. *J Clin Oncol.* 2004; 22:2371. [PubMed: 15197198]
14. Saroha S, Uzzo RG, Plimack ER, et al. Lymphopenia is an independent predictor of inferior outcome in clear cell renal carcinoma. *J Urol.* 2013; 189:454. [PubMed: 23041457]
15. Rosner I, Bratslavsky G, Pinto PA, et al. The clinical implications of the genetics of renal cell carcinoma. *Urol Oncol.* 2009; 27:131. [PubMed: 19285230]
16. Canter D, Kutikov A, Manley B, et al. Utility of the R.E.N.A.L. nephrometry scoring system in objectifying treatment decision-making of the enhancing renal mass. *Urology.* 2011; 78:1089. [PubMed: 22054378]
17. Novara G, Martignoni G, Artibani W, et al. Grading systems in renal cell carcinoma. *J Urol.* 2007; 177:430. [PubMed: 17222604]
18. Edge SB.; B, D.; Compton, CC., et al. *AJCC Cancer Staging Manual.* 7th. New York, NY: Springer-Verlag; 2010.
19. Sukov WR, Lohse CM, Leibovich BC, et al. Clinical and pathological features associated with prognosis in patients with papillary renal cell carcinoma. *J Urol.* 2012; 187:54. [PubMed: 22088335]
20. Delahunt B, Eble JN. Papillary renal cell carcinoma: a clinicopathologic and immunohistochemical study of 105 tumors. *Mod Pathol.* 1997; 10:537. [PubMed: 9195569]
21. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet.* 2001; 357:539. [PubMed: 11229684]
22. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002; 420:860. [PubMed: 12490959]
23. Kondo T, Ito F, Nakazawa H, et al. High expression of chemokine gene as a favorable prognostic factor in renal cell carcinoma. *J Urol.* 2004; 171:2171. [PubMed: 15126779]
24. Sejima T, Iwamoto H, Morizane S, et al. The significant immunological characteristics of peripheral blood neutrophil-to-lymphocyte ratio and Fas ligand expression incidence in nephrectomized tumor in late recurrence from renal cell carcinoma. *Urol Oncol.* 2013; 31:1343. [PubMed: 22153754]
25. Ohno Y, Nakashima J, Ohori M, et al. Pretreatment neutrophil-to-lymphocyte ratio as an independent predictor of recurrence in patients with nonmetastatic renal cell carcinoma. *J Urol.* 2010; 184:873. [PubMed: 20643463]

26. Pichler M, Hutterer GC, Stoeckigt C, et al. Validation of the pre-treatment neutrophil-lymphocyte ratio as a prognostic factor in a large European cohort of renal cell carcinoma patients. *Br J Cancer*. 2013; 108:901. [PubMed: 23385728]
27. Santoni M, De Giorgi U, Iacovelli R, et al. Pre-treatment neutrophil-to-lymphocyte ratio may be associated with the outcome in patients treated with everolimus for metastatic renal cell carcinoma. *Br J Cancer*. 2013
28. de Martino M, Pantuck AJ, Hofbauer S, et al. Prognostic Impact of Preoperative Neutrophil-To-Lymphocyte Ratio in Localized Nonclear Cell Renal Cell Carcinoma. *J Urol*. 2013
29. Ohno Y, Nakashima J, Ohori M, et al. Followup of neutrophil-to-lymphocyte ratio and recurrence of clear cell renal cell carcinoma. *J Urol*. 2012; 187:411. [PubMed: 22177153]
30. Jagdev SP, Gregory W, Vasudev NS, et al. Improving the accuracy of pre-operative survival prediction in renal cell carcinoma with C-reactive protein. *Br J Cancer*. 2010; 103:1649. [PubMed: 21063409]

Figure 1.

a) ALC distribution within the cohort. Kaplan-Meier curves demonstrating difference in overall survival among PRCC patients with b) ALC < 1.3 cell/ μ l vs. ALC $\geq$ 1.3 cells/ μ l and c) M0 patients. d) Cumulative incidence plot demonstrating cancer-specific survival among PRCC patients with ALC < 1.3 cells/ μ l vs. ALC $\geq$ 1.3 cells/ μ l.

Table 1

ALC and Patient Characteristics

			ALC					ALC <1.3		
	N	%	Mean	Median	Min	Max	p-value	N	%	p-value
Overall	192		1.6	1.6	0.5	3.5		56	29.2	0.730
PRCC type							0.420			
I	86	44.8	1.7	1.6	0.5	2.9		24	27.9	
II	106	55.2	1.6	1.5	0.7	3.5		32	30.2	
T stage							0.016			0.002
T1	128	66.7	1.6	1.7	0.5	3.5		27	21.1	
T2	25	13	1.4	1.5	0.8	2.9		9	36.0	
T3	36	18.8	1.3	1.4	0.7	2.7		18	50.0	
T4	3	1.6	1.0	1.3	0.9	2		2	66.7	
N stage							0.120			0.580
N0	175	91.2	1.6	1.7	0.5	3.5		50	28.6	
N1	17	8.8	1.4	1.4	0.8	2.5		6	35.3	
M stage							0.082			0.790
M0	174	90.6	1.6	1.7	0.5	3.5		50	28.7	
M1	18	9.4	1.4	1.4	0.8	2.5		6	33.3	
TNM stage							0.012			0.005
I	123	64.1	1.6	1.7	0.5	3.5		26	21.1	
II	24	12.5	1.4	1.5	0.8	2.9		9	37.5	
III	26	13.5	1.2	1.4	0.7	2.7		14	53.9	
IV	19	9.9	1.4	1.4	0.8	2.5		7	36.4	
Age at surgery							0.001			0.073
<60	75	39.1	1.7	1.8	0.6	3.5		16	21.3	
>60	117	60.9	1.5	1.5	0.5	2.9		40	34.2	
Gender							0.035			0.471
F	49	25.5	1.7	1.8	0.6	3		12	24.5	
M	143	74.5	1.5	1.6	0.5	3.5		44	30.8	
CCI (weighted)							0.017			0.004

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	ALC										ALC <1.3	
	N	%	Mean	Median	Min	Max	p-value	N	%	p-value		
<2	104	54.2	1.7	1.6	0.5	3.5	0.052	21	20.2	0.631		
>2	88	45.8	1.5	1.4	0.7	3.0		35	39.8			
Smoking History												
Never	79	41.2	1.5	1.5	0.5	2.9		25	31.7			
Ever	113	58.8	1.7	1.7	0.7	3.5		31	27.4			

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2
Results of Cox proportional hazards regression for time from surgery to All-Cause Mortality among PRCC patients

	Univariable Analysis				Multivariable Analyses			
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI
ALC	<1.3 vs. 1.3	2.43	1.33-4.46	0.004	2.28	1.21-4.28	0.011	
PPRC type	II vs. I	4.28	2.11-8.67	<0.001	2.03	0.90-4.56	0.086	
TNM Stage	II vs. I	1.54	0.50-4.68	0.450	1.13	0.36-3.53	0.838	
	III vs. I	5.31	2.33-12.07	<0.001	3.16	1.28-7.78	0.012	
	IV vs. I	26.62	11.39-62.21	<0.001	20.01	7.85-51.03	<0.001	
Age	<60 vs. 60	2.37	1.13-4.96	0.022	1.79	0.84-3.80	0.130	
CCI	2< vs. 2	1.34	0.73-2.47	0.344	-			
Smoking	any vs. none	1.90	0.99-3.65	0.053	-			

Table 3
Results of Cox proportional hazards regression for time from surgery to Cause-Specific Mortality among PRCc patients

	Univariable Analyses				Multivariable Analysis		
	HR	95% CI	p-value	sHR	95% CI	p-value	
ALC	<1.3 vs. 1.3	2.30	1.05 - 5.04	0.038	2.19	0.94-5.11	0.071
PPRC type	II vs. I	8.96	2.68 - 29.94	<0.001	3.30	1.04-10.51	0.043
TNM Stage	II vs. I	1.25	0.14-11.31	0.842	0.84	0.11-6.53	0.867
	III vs. I	11.59	3.68-36.52	<0.001	5.37	1.65-17.42	0.005
	IV vs. I	45.20	13.89-147.1	<0.001	30.46	10.24-90.63	<0.001
Age	<60 vs. 60	3.08	1.17 - 8.08	0.023	1.85	0.67-5.09	0.235
CCI	<2 vs. 2	1.40	0.58 - 3.38	0.451	--	--	--
Smoking	any vs. none	1.09	0.50 - 2.38	0.828	--	--	--

Table 4

Estimated overall survival at 36 months.

	ALC <1.3 / μ L		ALC $\geq$ 1.3 / μ L	
	N	%OS (95% CI)	N	%OS (95% CI)
All	51	75.9 (60.4-86.0)	125	87.2 (79.3-92.3)
Stage I-II	35	93.1 (74.6-98.3)	102	94.2 (86.4-97.6)
Stage III-IV	16	35.9 (12.3-60.6)	23	55.8 (31.9-74.3)
M0 only	46	82.9 (67.1-91.6)	114	92.8 (85.4-96.5)