Original Article

# The impact of histology on survival for patients with metastatic renal cell carcinoma undergoing cytoreductive nephrectomy

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## ABSTRACT

**Objective:** To evaluate the impact of histology on cancer-specific and overall survival for patients with metastatic renal cell carcinoma (mRCC) undergoing cytoreductive nephrectomy (CN).

**Materials and Methods:** We retrospectively reviewed the data of 505 patients with mRCC who underwent CN at Mayo Clinic, Rochester, MN, USA, between 1970 and 2008. All specimen were re-reviewed by a single genitourinary pathologist. Survival was estimated using the Kaplan–Meier method and compared according to histology with the log-rank test. Cox proportional hazard regression models were used to evaluate the association of histology with outcome.

**Results:** Forty (8%) patients with non-clear cell histology and 465 (92%) patients with clear cell histology were identified. The median follow-up was 7.8 years. Metastatic non-clear cell histology was associated with a significantly older median age at nephrectomy (66 vs. 60 years; $P = 0.002$), larger median tumor size (11.5 vs. 9.2 cm; $P = 0.02$), and higher rate of lymph node involvement (50% vs. 16%; $P < 0.001$). No significant difference in 3-year cancer-specific survival (25% vs. 22%; $P = 0.50$) was noted between patients with clear cell and non-clear cell histology. On multivariate analysis, non-clear cell histology was not significantly associated with patients' risk of death from cancer (HR 0.96; 95% CI 0.61, 1.51; $P = 0.85$).

**Conclusions:** Non-clear cell histology was not independently associated with adverse survival for patients with mRCC undergoing CN. As such, we advocate that surgical resection should continue to be considered in the multimodal treatment approach to these patients, while additional efforts to risk stratify and optimize management in this setting remain necessary.

**Key word**: Histology, kidney cancer, metastasis, nephrectomy, renal cell carcinoma

## INTRODUCTION

The incidence of renal cell carcinoma (RCC) in the United States in 2013 is expected to be 65,150, accounting for 3-5% of adult malignancies.[1] Approximately 20-30% of patients with renal cell carcinoma (RCC) present with metastatic disease.[2] Established prognostic features for patients with metastatic renal cell carcinoma (mRCC) include laboratory values, performance status, lymph node status, presence of sarcomatoid features as well as number and location of metastases.[3-5] The current treatment paradigm for patients with mRCC most frequently involves a multimodal approach, combining surgery in the form of CN with systemic therapy.[6,7]

Notably, the importance of tumor histology in the setting of mRCC remains to be established. In particular, while several series have to date evaluated the responsiveness of metastatic non-clear cell RCC (non-ccRCC) to targeted therapies, the independent prognostic value of histology among patients undergoing CN has not been definitively determined, largely due to the high relative prevalence of clear cell RCC (ccRCC) in metastatic disease.[8-14]

Histologic subtype has, on the other hand, been extensively evaluated for patients with clinically localized RCC, and, of note, ccRCC has largely but not universally been associated with adverse outcomes compared with non-ccRCC for

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these tumors.[15-21] At the same time, however, histology was not found to be independently associated with outcome in patients with locally advanced tumors.[22] Here, then, we evaluated the clinicopathologic outcomes of patients undergoing CN found to have non-ccRCC and compared the survival with patients with metastatic ccRCC.

## MATERIALS AND METHODS

After obtaining Institutional Review Board approval, we reviewed the Mayo Clinic Nephrectomy Registry to identify 505 patients who were treated with nephrectomy for sporadic, unilateral RCC, which was metastatic at presentation, between 1970 and 2008. Nephrectomy was performed by various surgeons over the time frame of the study using standard techniques. One urologic pathologist (JCC) re-reviewed all nephrectomy pathology specimens. Tumor staging followed the 2010 American Joint Committee on Cancer/Union Internationale Contre le Cancer 7th edition TNM classification.[23] Histology was assigned according to the American Joint Committee on Cancer, Union Internationale Contre le Cancer and Heidelberg guidelines.[24] Clinicopathologic variables recorded for analysis included age, gender, clinical presentation, Eastern Cooperative Oncology Group (ECOG) performance status, pathologic tumor stage, histologic subtype, nuclear grade, coagulative tumor necrosis, sarcomatoid differentiation and lymph node status.

The retrospective nature of this study precluded a standardized follow-up protocol in all patients. However, vital status for patients in the Nephrectomy Registry is updated each year. Vital status was identified from death certificates or physician correspondence. For patients followed elsewhere, the Mayo Clinic Nephrectomy Registry monitors outcomes annually by correspondence to the patient and the treating physician.

Continuous features were summarized with means, medians and ranges; categorical features were summarized with frequency counts and percentages. Comparisons of features between patients with ccRCC and non-ccRCC were evaluated using two-sample t, Wilcoxon rank sum, Chi-square, Fisher exact and Cochran–Armitage trend tests as appropriate. Overall survival (OS) and cancer-specific survival (CSS) were estimated using the Kaplan–Meier method and compared with the log-rank test. Associations of features with time to death were evaluated using Cox proportional hazards regression models, and summarized with hazard ratios and 95% confidence intervals. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC, USA). All tests were two-sided, with a $P$ value < 0.05 considered statistically significant.

## RESULTS

In total, 465 patients (92%) with ccRCC and 40 patients (8%) with non-ccRCC who underwent CN were identified. Non-ccRCC histology included papillary RCC ($n$ = 23), chromophobe RCC ($n$ = 8), collecting duct tumors ($n$ = 2) and unclassified RCC ($n$ = 7). Patient clinicopathologic demographics are summarized in Table 1. As can be seen, relative to patients with ccRCC, patients with non-ccRCC were significantly older at CN (66 vs. 60 years; $P$ = 0.002), with a larger median tumor size (11.5 vs. 9.2 cm; $P$ = 0.02) and more frequent lymph node involvement (50% vs. 16%; $P$ < 0.001). Furthermore, patients with non-ccRCC were more likely to have undergone metastasectomy than patients with ccRCC (55% vs. 37%; $P$ = 0.02).

Median follow-up after nephrectomy for those alive at the last follow-up was 7.8 years (range 0.5-18.7 years) for patients with non-ccRCC compared with 9.6 years (range 0.1-25.1 years) for the ccRCC cohort. During this time, 36 patients with non-ccRCC died, with 33 dying of RCC at a mean of 1.4 years following surgery (range 0.1-7.3 years). Meanwhile, 442 ccRCC patients died at a mean of 1.9 years following surgery (range 0.0-14.0), with 413 dying of RCC. Notably, 3-year CSS (22% vs. 25%; $P$ = 0.5) [Figure 1] and OS (24% vs. 18%; $P$ = 0.39) [Figure 2] were not significantly different between patients with non-ccRCC and ccRCC. Of note, 13 (33%) patients with non-ccRCC were treated with systemic therapy after CN, including four who received targeted therapy, while 218 of the ccRCC patients received systemic therapy post-operatively, with 40 receiving targeted agents ($P$ = 0.08).

To further investigate the independent association of tumor histology with survival, multivariable analysis was performed adjusting for patient performance status, regional lymph node involvement, sarcomatoid differentiation, number of sites of metastases and whether the patient underwent metastasectomy [Table 2]. Here, again, RCC histologic subtype was not found to be significantly associated with patients' risk of death from RCC ($P$ = 0.85).

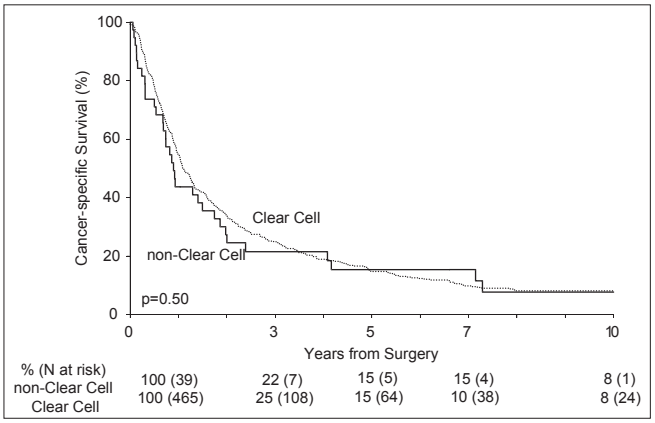


**Figure 1:** Kaplan–Meier curve comparing cancer-specific survival following cytoreductive nephrectomy for patients with non-clear cell renal cell carcinoma compared with clear cell renal cell carcinoma

**Table 1: Clinicopathologic features of patients with non-ccRCC versus patients with ccRCC**

| Variables | Median (range) | | *P* value |
|---|---|---|---|
| | Non-ccRCC *N*=40 | ccRCC *N*=465 | |
| Age at surgery (years) | 66 (31–82) | 60 (25–88) | 0.002 |
| Tumor size (cm; *N*=497) | 11.5 (1.5–24.5) | 9.2 (2.1–23.0) | 0.02 |
| Sex | | *N* (%) | |
| Female | 9 (23) | 151 (32) | 0.19 |
| Male | 31 (78) | 314 (68) | |
| Symptoms at presentation | 26 (65) | 355 (76) | 0.11 |
| ECOG performance status (*N*=349) | | | |
| 0 | 19 (66) | 248 (78) | 0.42 |
| 1 | 8 (28) | 55 (17) | |
| 2 | 2 (7) | 8 (3) | |
| 3 | 0 | 8 (3) | |
| 4 | 0 | 1 (<1) | |
| 2010 primary tumor classification (*N*=500) | | | |
| pT1a | 2 (5) | 17 (4) | 0.15 |
| pT1b | 3 (8) | 50 (11) | |
| pT2a | 2 (5) | 49 (11) | |
| pT2b | 5 (13) | 39 (8) | |
| pT3a | 14 (35) | 202 (44) | |
| pT3b | 6 (15) | 54 (12) | |
| pT3c | 2 (5) | 11 (2) | |
| pT4 | 6 (15) | 38 (8) | |
| 2010 regional lymph node involvement | | | |
| pNx | 16 (40) | 283 (61) | <0.001 |
| pN0 | 4 (10) | 107 (23) | |
| pN1 | 20 (50) | 75 (16) | |
| Nuclear grade | | | |
| 1 | 0 | 10 (2) | 0.07 |
| 2 | 4 (10) | 70 (15) | |
| 3 | 20 (50) | 255 (55) | |
| 4 | 16 (40) | 130 (28) | |
| Coagulative tumor necrosis | 31 (78) | 296 (64) | 0.08 |
| Sarcomatoid differentiation | 10 (25) | 82 (18) | 0.25 |
| Number of sites of distant metastases | | | |
| 1 | 29 (73) | 340 (73) | 0.42 |
| 2 | 6 (15) | 100 (22) | |
| □3 | 5 (13) | 25 (5) | |

ccRCC=Clear cell RCC, ECOG=Eastern cooperative oncology group

**Table 2: Multivariate Cox proportional hazards regression analysis of factors associated with death from RCC among patients with non-ccRCC versus ccRCC treated with cytoreductive nephrectomy**

| Feature | Hazard ratio (95% CI) | *P* value |
|---|---|---|
| ECOG performance status | | |
| 0 | 1.0 (reference) | 0.36 |
| □1 | 1.13 (0.87–1.49) | |
| 2010 regional lymph node involvement | | |
| pNx/pN0 | 1.0 (reference) | <0.001 |
| pN1 | 1.73 (1.29–2.32) | |
| Sarcomatoid differentiation | 1.76 (1.32–2.35) | <0.001 |
| Number of sites of distant metastases | 1.21 (1.00-1.46)* | 0.05 |
| Surgery for at least one distant metastases | | |
| No | 1.0 (reference) | 0.02 |
| Yes | 0.75 (0.59–0.96) | |
| Histologic subtype | | |
| Clear cell RCC | 1.0 (reference) | 0.85 |
| Non-clear cell RCC | 0.96 (0.61–1.51) | |

*Hazard ratio represents a 1-unit increase in number of sites of distant metastases.CI=Confidence interval, RCC=Renal cell carcinoma, ccRCC=Clear cell RCC, ECOG=Eastern cooperative oncology group

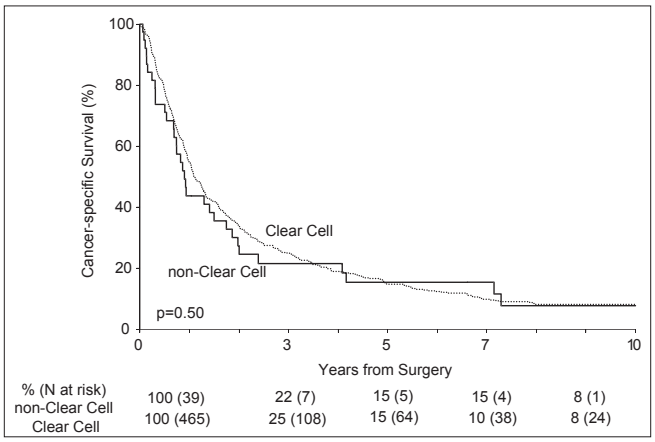


**Figure 2:** Kaplan–Meier curve comparing overall survival following cytoreductive nephrectomy for patients with non-clear cell renal cell carcinoma compared with clear cell renal cell carcinoma

## DISCUSSION

We found that patients with metastatic non-ccRCC frequently present with adverse pathologic features, including larger tumor size and more frequent lymph node invasion, than patients with metastatic ccRCC. However, we noted further that tumor histology was not independently associated with CSS or OS following CN. Our study of patients with metastatic non-ccRCC is notable in that (1) all patients here underwent CN, (2) all specimens underwent pathologic re-review to confirm histology and (3) adverse pathologic features that might obscure the ability to discern an independent impact of histology with survival following nephrectomy were controlled for multivariate analyses.

Cytoreductive nephrectomy currently remains an important component to the multimodal treatment approach for

patients with mRCC. A survival benefit to surgery in patients receiving systemic treatment was demonstrated by two randomized trials in the cytokine era.[6,7] Moreover, CN alone has demonstrated a 1-, 2-, 5- and 10-year OS rate increase of 35.1%, 28.9%, 17.1% and 11.5%, respectively, relative to no surgery.[25] In addition, retrospective population-based data have indicated that for patients treated with tyrosine kinase inhibitors for mRCC, prior nephrectomy was independently associated with improved survival.[26] Indeed, the majority of patients (67-100%) in trials supporting the use of targeted therapy in mRCC had undergone nephrectomy prior to initiation of therapy, further suggesting a value for surgical resection in the management of mRCC for appropriately selected patients.[9,27-30]

The interaction of histology with outcome in RCC remains complex. That is, ccRCC has been largely but not universally associated with adverse survival among patients with localized RCC.[15-21] In the setting of mRCC, however, prior reports have demonstrated that while the frequency of metastatic disease may be less for non-ccRCC than for ccRCC, adverse survival has been associated with metastatic non-ccRCC compared with metastatic ccRCC.[8,10,11] For example, Motzer *et al*., in a report of 64 patients with metastatic non-ccRCC (of whom 52 had a prior nephrectomy), found a median survival of 9.4 months (range 8-14 months).[8] Of note, the predominant histology in that series was collecting duct (41%), which is associated with the poorest prognosis and with its relative rare description compromised an usually high proportion of cases.[15] Likewise, Ronnen *et al*. reported on 38 patients with metastatic papillary RCC, of whom 74% ($n = 28$) had a prior nephrectomy, and observed a median survival of 8 months (range 5-12 months).[10]

Meanwhile, Kassouf and colleagues retrospectively compared 94 patients with non-ccRCC with 514 patients with ccRCC who underwent CN.[11] Non-ccRCC patients were younger at the time of CN (54 vs. 57 years; $P = 0.0001$), and were more likely to have nodal metastases (77% vs. 26%; $P < 0.0001$) and sarcomatoid features (23% vs. 13%; $P = 0.03$).[11] None of the patients in the non-ccRCC cohort underwent metastasectomy, although 90% of the patients received post-operative systemic therapy, including six patients treated with targeted therapy. These investigators found that patients with non-ccRCC had a significantly shorter median CSS than patients with ccRCC (9.7 vs. 20.3 months; $P = 0.0003$).[11]

Similar to the aforementioned study,[11] we noted that patients with metastatic non-ccRCC were more likely to have regional lymph node involvement than patients with metastatic ccRCC. However, in our data, non-ccRCC patients were older at CN and had larger median tumor size. Furthermore, we found that patients with non-ccRCC were more likely to undergo metastasectomy than patients with ccRCC. Importantly, we did not observe a significant difference in survival between patients with metastatic non-ccRCC and ccRCC, and, on multivariate analysis, non-ccRCC histology was not significantly associated with patients' risk of death from RCC ($P = 0.85$). A potential explanation for the disparate survival outcome noted here vs. the study by Kassouf *et al*. may be that in our series, patients with non-ccRCC were more likely to undergo metastasectomy, which has been associated with improved survival among patients with mRCC.[4]

We recognize as well that our study is limited by its retrospective non-randomized design. Moreover, given the tertiary referral nature of our practice, many patients received at least part of their follow-up locally, which introduces heterogeneity into surveillance modalities/frequency. Additionally, given the time-frame of our analysis, only a minority of patients were treated with targeted therapies after CN, which may have impacted our ability to discern a difference in survival between metastatic ccRCC and non-ccRCC patients, as evidence has suggested that tyrosine kinase inhibitors have lower levels of activity in papillary RCC compared with ccRCC.[12] Indeed, studies by Tannir *et al*. and Choueiri *et al*. noted a lower response rate of non-ccRCC to tyrosine kinase inhibitors.[13,14] While we must acknowledge the critical importance of further developments in systemic therapies for non-ccRCC histology, we did not find an association of histology with outcome in the setting of advance disease. As such, we believe that aggressive surgical resection should continue to be considered for patients with metastatic non-ccRCC in whom the value of CN has previously been questioned.

## CONCLUSION

Patients undergoing CN for non-ccRCC were significantly older, with a larger median tumor size and a higher incidence of nodal metastases. Nevertheless, no difference was noted according to histology in CSS or OS. In addition, non-clear cell histology was not independently associated with patients' risk of death from RCC. We, therefore, advocate that surgical resection should continue to be considered in the multimodal treatment approach to these patients, while additional efforts to risk stratify and optimize management in this setting remaining necessary.

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Dharam Kaushik, MBBS and Manuel S. Eisenberg, M. D.

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