Case Series

Impact of Histology and Tumor Grade on Clinical Outcomes Beyond 5 Years of Follow-Up in a Large Cohort of Renal Cell Carcinomas

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Abstract

Introduction: The optimal length for clinical follow-up of renal cell carcinoma (RCC) patients is unclear. We evaluated the impact of ISUP/WHO tumor grade and histological subtype on short- and long-term survival and risk of recurrence/metastasis in a large cohort of RCC patients. **Patients and Methods:** We studied 1679 RCC patients from a single referral center in Italy. Adjusted hazard ratios for overall survival were estimated using Cox regression models. Adjusted absolute risk of developing recurrence or metastasis was computed considering competing risks of mortality. **Results:** During up to 13 years of follow-up, 175 (10.4%) RCC patients died, of whom 92% beyond 5 years. Hazard ratio of grade IV clear cell carcinomas (ccRCC) was 3.82 compared to grade II. Notably, 33% of recurrences and 56% of distant metastases occurred beyond 5 years of follow-up. The estimated probabilities of recurrence/metastasis were 15% and 45% within and beyond 5 years of follow-up, respectively. After 5 years, the absolute risk of recurrences increased also for papillary renal cell carcinoma type I (35.2%) and grade I ccRCC (17%). **Conclusion:** After 5 years of follow-up, both risk of mortality and recurrences or metastases were high and were modified by histological types and tumor grade. These data strongly support histology- and grade-tailored surveillance strategies and long-term follow-up for RCC patients.

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Introduction

In the United States, approximately 74,000 new cancer cases occurring in kidney and renal pelvis have been estimated in 2020,[1] with the vast majority of these (90%) being renal cell carcinomas (RCC). RCC incidence rates have been increasing worldwide and are highest in Western countries, particularly North America and most countries in Europe.[2]

RCC originates in the kidney proximal convoluted tubules and includes several histological subtypes with distinct prognosis,[3] such as clear cell (ccRCC, ~70%), papillary (pRCC, ~10%-15%), chromophobe (chrRCC, ~5%) as well as rarer types like collecting duct carcinomas (cdRCC, ~1%).

Abbreviations: AUA, American Urological Association; ccRCC, clear cell renal cell carcinoma; cdRCC, collecting duct renal cell carcinoma; chrRCC, chromophobe renal cell carcinoma; CI, confidence interval; EAU, European Association of Urology; HRs, adjusted hazard ratios; ISUP, International Society of Urological Pathology; NCCN, National Comprehensive Cancer Network; pRCC, papillary renal cell carcinoma; RCC, renal cell carcinomas; WHO, World Health Organization.

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In 2012, the International Society of Urological Pathology and the World Health Organization (ISUP/WHO) tumor grade classification system[4] was introduced and was found to be associated with RCC survival,[5,6] but data on the association with risk of recurrence or metastasis are sparse.[7,8] Moreover, the optimal follow-up length for RCC patients remains unclear and needs to be elucidated as acknowledged by the major RCC surveillance guidelines from the European Association of Urology (EAU), American Urological Association, and National Comprehensive Cancer Network (NCCN).[3,9] Five years after surgery is the typical follow-up length, but clinicians have suggested longer follow-up[10,11], and the rates of recurrence have shown to remain elevated beyond the 5-year endpoint in a few studies with limited details on histological subtypes.[12,13]

Here we report the impact of tumor histology and grade on RCC survival and absolute risk (ie, cumulative incidence) of recurrence or metastasis, in a large patient cohort followed for up to 13 years from surgery at a single institution with advanced clinical care.

Patients and Methods

We reviewed records of 1947 patients treated between January 1, 2001 and November 30, 2016 at the Regina Elena National Cancer Institute, Rome, Italy. We excluded 268 oncocytoma and focused only on patients with malignant lesions (n = 1679). All patients included in this analysis were of European descent, 18-85 years old at diagnosis, with a pathologically confirmed renal malignancy (ICD-10 code C64). Every patient signed an informed consent form approved by the hospital Institutional Review Board.

Tumor characteristics, clinical outcomes, and medical/surgical treatments were recorded by a single team of surgeons, with pathology review of all RCC tumors. Histological subtypes included ccRCC, pRCC, chrRCC, cdRCC and other rare or mixed subtypes. We further classified ccRCC into ISUP/WHO-grades I-IV and pRCC into types I (pRCC1) and II (pRCC2),[14] respectively. Follow-up for outcome (disease progression, relapse, vital status, and cause of death) was performed by medical examinations or alternatively by telephone call to the patients or their relatives every 3, 6 and 12 months after the first year from diagnosis, and then every 6 months until the fifth year from the initial diagnosis. For the remaining 5 years, patients with aggressive subtypes (based on histology, stage and grade) were followed every 6 months, otherwise yearly. For subjects who developed a local recurrence or metastasis and underwent surgery, follow-up was extended beyond 10 years at least once a year. Confirmation of vital status beyond active follow-up was obtained approximately every 2 years via medical record assessment and calls to relatives. We computed Kaplan-Meier and lifetable estimates and fitted Cox models to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for all-cause mortality and for a combined estimate of recurrence and metastasis after surgery. Only new events occurring 3 months after surgery, including cases exhibiting metastasis at diagnosis, have been considered. Follow-up began at the time of surgery and ended at the earliest of time of death or lost-to-follow-up (ie, the last known follow-up visit or therapy). One hundred fifty-seven patients (9.4%) with incomplete follow-up information were not included in the analysis. Their demographic and clinical characteristics were similar to those included in the study (Supplementary Table S1).

For Kaplan-Meier, lifetable and Cox models with recurrence/metastasis as outcome, death was treated as a censoring event. Estimates of absolute risk of first recurrence/metastasis accounting for competing mortality risk were obtained based on a cause-specific formulation.[15] All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and R software.

Results

Patient and Tumor Characteristics

The characteristics of the 1679 patients are shown in Supplementary Table S2 (overall) and Table S3 (by histologic subtypes). Over two-thirds of patients were male (67.1%). The histological subtypes included 75.1% ccRCC, 7.5% pRCC1, 3.9% pRCC2, 7% chrRCC, and 1% cdRCC; most ccRCC had grades II or III. Tumor size was <4 cm in 41% of tumors. After surgery, 3.2% of patients with known recurrence status had a local recurrence in the renal lodge, adrenal gland or loco-regional lymph nodes, 4.7% a renal parenchymal recurrence, and 18.6% developed distant metastases (Table S3). Tumor size, stage, necrosis, venous thrombosis, recurrences and metastases increased with increasing grade in ccRCC. While thrombosis and metastases were higher in pRCC2 than pRCC1, necrosis and recurrences did not differ between these types (Table S3).

Survival and Absolute Risk of Recurrence and Metastasis Stratified by RCC Histological Subtypes

In Cox models, stage, tumor size, age at surgery, histology, sex, and thrombosis were significantly associated with overall survival; stage, age, sex, tumor necrosis and size were significantly associated with risk of metastasis/recurrence. Associated variables were included in the final models, except for necrosis, which had 46.8% of missing values. For the analysis of ccRCC by grade, the models were adjusted for age and stage. We also assessed associations of grade with overall survival and recurrence/metastasis in analyses stratified by stage.

During follow-up, 175 (10.4%) RCC patients died, of whom 92% (161/175) after 5 years of follow-up. Most (85.4%) deaths were due to renal cancer. For grade I ccRCC, grade IV ccRCC and pRCC2 the unadjusted probabilities of overall death were 0%, 27% and 15%, respectively within 5 years, and 0%, 31% and 35%, after 5 years of follow-up. The probability of having an event before 5 years is 1 – surviving past 5 years and the probability of death after 5 years is computed from the tables as P(surviving past the last time point)/P(surviving past 5 years) (Table S4). In adjusted Cox model survival analysis (Figure 1A), cdRCC had the worst (all died within one year) with an HR 5.60 (95% CI 2.55-12.3), and chrRCC the best prognosis (HR = 0.30, 95% CI 0.07-1.23) (Table S5A). The survival probabilities were clearly distinct when stratifying ccRCC by grade ($P < .0001$) and pRCC by type ($P < .0001$) (Figure 1B; Table S5B). Among ccRCC, HRs for grades III and IV vs. grade II were 2.24 (95% CI 1.38-3.63) and 3.92 (95% CI 2.17-7.07), respectively, when computed over the whole follow-up period.

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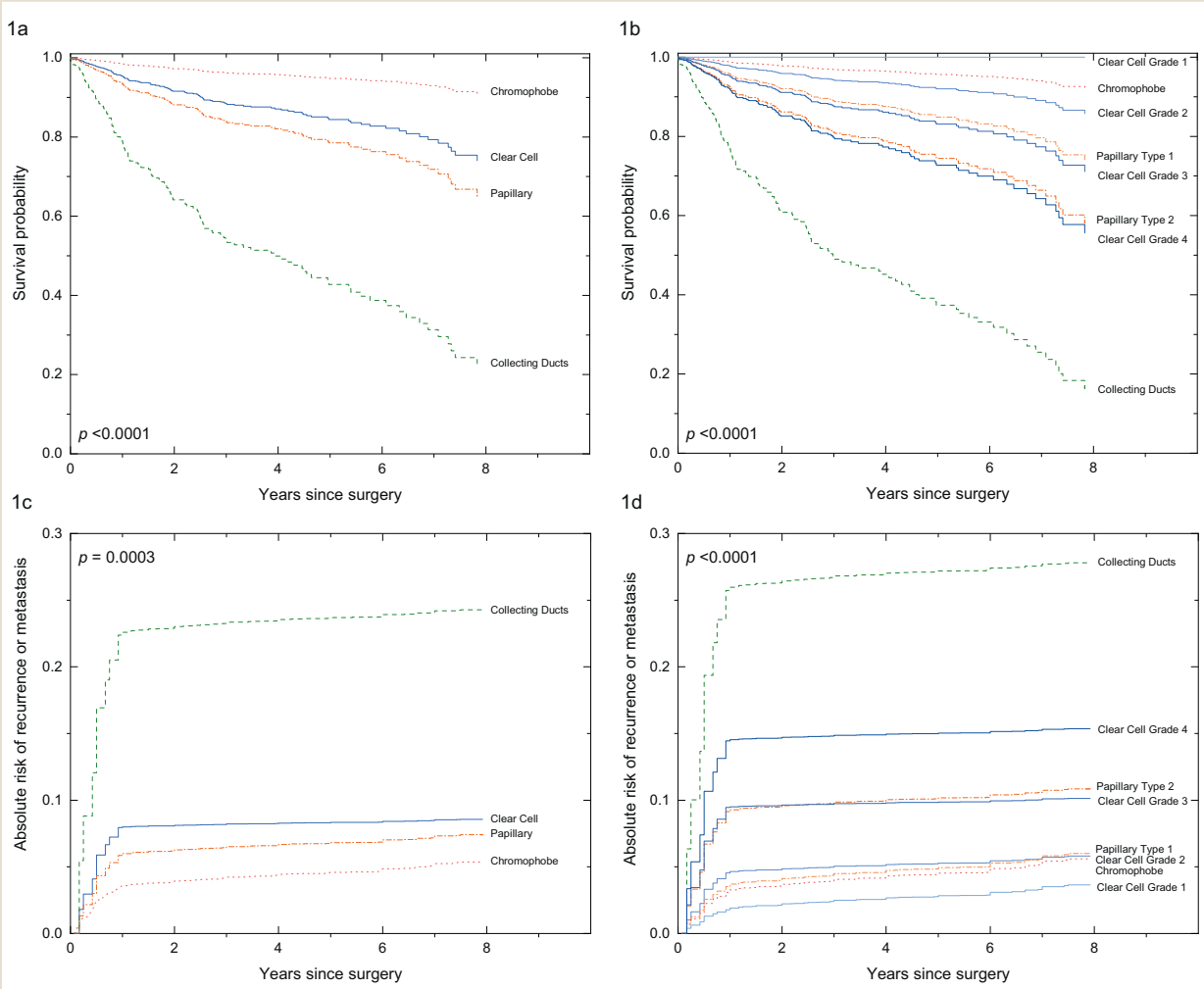
Figure 1 **Overall survival curves and absolute risk estimates for death from any cause and recurrence or metastasis. Panels A and B: Survival curves by histology estimated from Cox proportional hazards models additionally adjusted for age, tumor size, stage, sex, and thrombosis. Panels C and D: Absolute risk of recurrence or metastasis by histology estimated from cause-specific Cox proportional hazards models additionally adjusted for age, tumor size, stage and sex. Panels B and D show clear cell renal cell carcinomas (ccRCC) further stratified by tumor grade and papillary renal cell carcinomas (pRCC) stratified by subtype. The plotted absolute risks are based on the profile of a female patient with grade 1, age <52 y, and tumor size less than 4 cm.**



Notably, 33% (38/119) of recurrences and 56% (156/276) of metastases occurred beyond 5 years of follow-up. Overall, the estimated probabilities of metastasis/recurrence were 15% and 45% [1-(0.47/0.85)] within and beyond 5 years of follow-up, respectively (Table 1). Major differences by tumor histology and grade were observed: during the first 5 years of follow-up, the recurrence/metastasis estimated probability ranged from 0% for ccRCC grade I or chRCC, to 87% for cdRCC (Table 1). After 5 years of follow-up, many recurrences/metastases were observed, even for histological types considered as less aggressive, like pRCC1 (35.2%) and ccRCC grade I (17%). Tumor grade strongly impacted the risk of recurrence/metastasis among ccRCC patients: the estimated probabilities within 5 years of follow-up were 0%, 7%, 22% and 52% for grades I, II, III, and IV, respectively. After 5 years, they were 17%, 32%, 66% and 78%, respectively. While overall ccRCC had low absolute risk of recurrences/metastases (Figure 1C; Table S5C), grade IV ccRCC had 3-fold higher absolute risk compared to grade II ccRCC over 8 years of follow-up (Figure 1D; Table S5D). Sensitivity analysis of recurrence/metastasis excluding 31 patients with positive surgical margins showed similar results (data not shown). Notably, among cases who had recurrences/metastases after 5 years almost 21% received radical nephrectomy (Table S6). Correspond-

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Table 1 Life Table Estimates for The Combined Outcome Recurrence/Metastasis Among Patients With Valid Follow-Up Information (N = 1434)

	Interval year of follow-up						
	Lower	Upper	Number of events	Number of censored observations	Proportion of events %	With no recurrence/metastasis %	No recurrence/metastasis Standard Error %
All histologies	0	1	190	323	0	100	0
	1	5	128	475	15	85	1.0
	5	9	33	236	31	69	1.5
	9	13	4	37	43	57	2.2
	13	–	1	0	53	47	4.9
Clear cell	0	1	160	245	0	100	0
carcinoma	1	5	110	360	16	84	1.1
	5	9	26	205	32	68	1.6
	9	13	4	33	43	57	2.3
	13	–	1	0	53	47	5.1
Clear cell	0	1	0	11	0	100	0
carcinoma	1	5	1	25	0	100	0
grade I	5	9	2	14	3	97	2.8
	9	13	0	5	17	83	9.4
	13	–	0	0	–	–	–
Clear cell	0	1	37	125	0	100	0
carcinoma	1	5	33	216	7	93	1.1
grade II	5	9	9	140	17	83	1.9
	9	13	2	18	24	76	2.9
	13	–	1	0	37	63	8.5
Clear cell	0	1	77	90	0	100	0
carcinoma	1	5	59	106	22	78	2.2
grade III	5	9	13	46	47	53	3.1
	9	13	2	9	61	39	4.1
	13	–	0	0	73	27	7.5
Clear cell	0	1	43	17	0	100	0
carcinoma	1	5	15	11	52	48	5.5
grade IV	5	9	2	4	79	21	5.2
	9	13	0	0	90	10	5.9
	13	–	0	0	–	–	–
Papillary	0	1	4	32	0	100	0
type I	1	5	3	49	4	96	2.0
	5	9	5	16	10	90	3.6
	9	13	0	3	38	62	10.7
	13	–	0	0	–	–	–
Papillary	0	1	14	12	0	100	0
type II	1	5	8	16	29	71	6.4
	5	9	2	3	56	44	8.5
	9	–	0	0	81	19	12.2
Chromophobe	0	1	2	33	0	100	0
	1	5	6	50	2	98	1.6
	5	9	0	12	16	84	5.2
	9	13	0	1	–	–	–
	13	–	0	0	–	–	–
Collecting duct	0	1	10	1	0	100	0
carcinoma	1	5	1	0	87	13	9.9
	5	–	–	–	–	–	–

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ing results, separately in patients with and without metastatic cancer at baseline are reported in Supplementary Tables S7 and S8, respectively.

In analyses stratified by stage, similar patterns of association for grade with ccRCC survival and recurrence/metastasis were observed. However, larger studies are needed because we had small numbers in some stage/grade groups that precluded our ability to draw meaningful conclusions (Table S9). Similarly, small numbers precluded analyses of pRCC by subtype.

Kaplan-Meier curves for overall survival and recurrence/metastasis are shown in supplementary Figures S1A and S1B, respectively. Overall, the median time to recurrence/metastasis was 10 years (95% CI 8.5-13.08). For ccRCC grades II and IV, median time was 12.42 and 0.83 years, respectively.

Discussion

The identification of an optimal follow-up length after RCC diagnosis and surgery is clearly needed,[3,9] as emphasized by the European and American urological associations and the National Comprehensive Cancer Network. In the current clinical setting, cancer patients are followed up to 5 years after surgery;yet, some studies suggest the need of a longer surveillance time since locoregional recurrence and metastases can occur at a significant rate also beyond this time point.[10,11]

In a large series of RCC patients followed for up to 13 years from surgery, we have shown that ISUP/WHO-grade and histology are important prognostic factors for both long-term survival and absolute risk of recurrence or metastasis. We observed 92% of deaths after the typical 5-year follow-up time. Similarly, after 5 years the overall probability of metastasis or recurrence was high, even for less aggressive histological subtypes, such as pRCC1 (35%) and grade I ccRCC (17%). For grade III and IV ccRCC the absolute risk of events was as high as 66% and 78%, respectively. Our data also showed that almost 21% of cases who had a recurrence/metastasis after 5 years received a radical nephrectomy, which supports conclusions found in another study.[16] Being from a tertiary cancer center, the cases who underwent radical nephrectomy examined in this manuscript may be more likely to have tumors with worse biology and higher recurrence rates.

These results can be used in the clinic to tailor treatment based on the probability of tumor recurrence/metastasis in the near and long-term future. Only a few studies reported follow-up data beyond 5 years from RCC diagnosis, and mostly focused on the clear cell renal cell carcinoma subtype.[12,13] One of the most recent and large study, the ECOG-ACRIN E2805 trial cohort showed that after 2 years of recurrence-free status, the risk remains stable even after 5 years from surgery, questioning the current practice of halting the follow-up at 60 months.[12] Our study supports these findings and extends them beyond the ccRCC subtype. Optimally, an extended follow-up beyond 5 years should be considered for all patients with malignant kidney cancers, although we acknowledge that by extending surveillance additional costs will be incurred[17] and a cost analysis should be considered. If adequate resources are available, our findings suggest that grade III and IV ccRCC patients should be followed longer than 5 years to capture more than 60% of events. Additionally, it would be important to follow patients with less aggressive subtypes such as pRCC1 and low-grade ccRCC because in time some patients develop recurrences or metastases (in our study, 35% and 17% for pRCC1 and grade I ccRCC, respectively).

Conclusions

In conclusion, our findings highlight the importance of extending follow-up of RCC patients beyond 5 years from surgery. The extended surveillance requires cost-effective approaches, and the knowledge of the impact of histology and tumor grade on survival and risk of metastasis or recurrence can aid in developing patient-tailored surveillance strategies.

Clinical Practice Points

- As argued by the surveillance guidelines for RCC from the EAU, AUA, and NCCN, the optimal follow-up length for RCC remains to be defined. Five years after surgery is the typical length, but some studies suggest the need of a longer surveillance time. In a large series of 1679 RCC patients followed for up to 13 years from surgery, 92% of deaths occurred after the typical 5-year of follow-up time, particularly for collecting duct carcinomas and high-grade ccRCC. After 5 years, the absolute risk of recurrences increased also for papillary renal cell carcinoma type I and grade I ccRCC. Our study strongly supports histology- and grade-tailored surveillance strategies and long-term follow-up for RCC patients.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2021.07.003.

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