A Novel Grading System for Clear Cell Renal Cell Carcinoma Incorporating Tumor Necrosis

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Abstract: Grading of renal cell carcinoma (RCC) has prognostic significance, and there is recent consensus by the International Society of Urological Pathology (ISUP) that for clear cell and papillary RCC, grading should primarily be based on nucleolar prominence. Microscopic tumor necrosis also predicts outcome independent of tumor grading. This study was undertaken to assess whether the incorporation of microscopic tumor necrosis into the ISUP grading system provides survival information superior to ISUP grading alone. Data on 3017 patients treated surgically for clear cell RCC, 556 for papillary RCC, and 180 for chromophobe RCC were retrieved from the Mayo Clinic Registry. Median follow-up periods were 8.9, 9.7, and 8.5 years, respectively. Four proposed grades were defined: grade 1: ISUP grade 1 + ISUP grade 2 without necrosis; grade 2: ISUP grade 2 with necrosis + ISUP grade 3 without necrosis; grade 3: ISUP grade 3 with necrosis + ISUP grade 4 without necrosis; grade 4: ISUP grade 4 with necrosis or sarcomatoid/rhabdoid tumors. There was a significant difference in survival between each of the grades for clear cell RCC, and the concordance index was superior to that of ISUP grading. The proposed grading system also outperformed the ISUP grading system when cases were stratified according to the TNM stage. Similar results were not obtained for papillary RCC or chromophobe RCC. We conclude that grading for clear cell RCC should be based on nucleolar prominence and necrosis, that ISUP grading should be used for papillary RCC, and that chromophobe RCC should not be graded.

Key Words: renal cell carcinoma, grade, necrosis, prognosis

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Grading of renal cell carcinoma (RCC) remains controversial, despite its designation as a category 1 prognostic factor (well supported by the literature; generally used in patient management) in the College of American Pathologists Working Classification for Prognostic Markers.[1,2] Of the numerous grading systems that have been proposed for these tumors, that of Fuhrman et al[3] has, until recently, been endorsed for routine clinical use.[4] Despite its widespread use, the Fuhrman system has methodological problems relating to its application, reproducibility, and validity, and more recently it has been recommended that for clear cell RCC and papillary RCC, grading should focus upon nucleolar prominence.[5,6] These issues were recently addressed by the International Society of Urological Pathology (ISUP) at an international consensus conference convened in Vancouver, Canada. At this meeting, attended by 133 urologic pathologists from 29 countries, it was agreed that for clear cell RCC and papillary RCC, nucleolar prominence alone should be adopted as the defining criteria for grade 1 to 3 tumors and that grade 4 be defined on the basis of extreme nuclear pleomorphism, including the presence of tumor giant cells.[7]

Although nucleolar grading provides prognostic information for clear cell RCC and papillary RCC, there is evidence to suggest that there is an overlap between different grades in their predictive power as prognostic indicators.[6] This has also been observed in studies relating to Fuhrman grading, in which significant differences in outcome between grades were achieved only when grades were grouped for analytical purposes.[8–10] Similarly, although sarcomatoid differentiation in RCC is recognized as a feature associated with poor prognosis,[11,12] there is uncertainty as to whether this differs from the poor outcome seen with tumors showing extreme nuclear pleomorphism, despite both being classified as grade 4 tumors on the basis of Fuhrman grading criteria.[3]

In previous studies microscopic tumor necrosis has been shown to have prognostic significance for clear cell and chromophobe RCC.[8,13–16] As the prognostic significance of microscopic necrosis has been shown to be independent of the nucleolar grade on multivariate analysis for clear cell RCC, this would seem to have potential application as a grading parameter for these tumors.

In view of this we have investigated a novel grading classification for RCC based on the ISUP grading

classification[5,7] and microscopic tumor necrosis. We have tested the utility of this grading system in separate series of clear cell, papillary, and chromophobe RCC to determine whether this grading system provides prognostic information superior to that of nucleolar grading alone.

MATERIALS AND METHODS

Patient Selection

After institutional review board approval, the Mayo Clinic Nephrectomy Registry was searched to identify 3834 patients treated with open or laparoscopic radical or partial nephrectomy for sporadic, unilateral, clear cell, papillary, or chromophobe RCC between 1970 and 2006. Eighty-one (2%) patients who died from an unknown cause were excluded, leaving 3753 patients for analysis.

Grading Criteria

Tumors were graded according to the recently endorsed ISUP grading system. The tumors were graded 1 to 3 according to the degree of nuclear prominence[8,10]—ie, grade 1: absent or inconspicuous nucleoli at ×400 magnification; grade 2: nucleoli conspicuous at ×400 magnification but inconspicuous or invisible at ×100 magnification; and grade 3: nucleoli conspicuous at ×100 magnification. Tumors showing extreme nuclear pleomorphism with or without multinucleate tumor giant cells were assigned grade 4, although tumors with a sarcomatoid or rhabdoid component were also assigned grade 4.

In addition to these features, the slides were reviewed for the presence or absence of microscopic coagulative tumor necrosis. Necrosis consisted of homogenous clusters of sheets of dead cells, or coalescing groups of cells forming a coagulum, containing nuclear and cytoplasmic debris as previously described.[16] Coagulative tumor necrosis was found to be present regardless of the area of tumor involved; the extent of involvement was not assessed. In the case of papillary RCC, the necrosis was often accompanied by cholesterol clefts and fibrinoid debris.

Statistical Methods

Comparisons of pathologic features by histologic subtype were made using χ^2 tests. Cancer-specific survival was estimated using the Kaplan-Meier method and compared among groups using log rank tests. Associations with death from RCC were further evaluated using Cox proportional hazards regression models and summarized with hazard ratios and 95% confidence intervals (CI). The ability of a feature to predict death from RCC was evaluated using the *c* (for concordance) index proposed by Harrell et al[17] The *c* index corresponds to the proportion of all suitable pairs of patients in whom the observed and predicted survival times are concordant. The *c* index is given by the area under a receiver operating characteristic curve. A *c* index of 1.0 indicates that the feature perfectly separates patients with different outcomes, whereas a value of 0.5 indicates that the feature contains prognostic information equal to that obtained by chance alone. *c* indexes were internally validated using a bootstrap methodology. Seventeen statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC). All tests were 2-sided, and *P*-values <0.05 were considered statistically significant.

TABLE 1. Comparisons of Pathologic Features by Histologic Subtype for 3753 Patients With RCC

	Histologic Subtype, N (%)			
Pathologic Feature	Clear Cell	Papillary	Chromophobe	*P*
ISUP grade				< 0.001
1	272 (9)	11 (2)	0	
2	1256 (42)	327 (59)	145 (81)	
3	1208 (40)	205 (37)	21 (12)	
4	281 (9)	13 (2)	14 (8)	
Necrosis				< 0.001
Absent	2119 (70)	315 (57)	147 (82)	
Present	898 (30)	241 (43)	33 (18)	
Sarcomatoid/rhabdoid				< 0.001
Absent	2851 (95)	546 (98)	166 (92)	
Present	166 (5)	10 (2)	14 (8)	
2010 primary tumor classification (N = 3727)				< 0.001
pT1a	820 (27)	272 (49)	46 (26)	
pT1b	683 (23)	139 (25)	44 (24)	
pT2a	329 (11)	45 (8)	30 (17)	
pT2b	163 (5)	35 (6)	37 (21)	
pT3a	711 (24)	45 (8)	18 (10)	
pT3b	189 (6)	11 (2)	1 (1)	
pT3c	37 (1)	2 (< 1)	0	
pT4	62 (2)	4 (1)	4 (2)	
2010 regional lymph node involvement				< 0.001
pNx	2307 (76)	486 (87)	141 (78)	
pN0	537 (18)	39 (7)	32 (18)	
pN1	173 (6)	31 (6)	7 (4)	
Distant metastases				< 0.001
M0	2566 (85)	537 (97)	172 (96)	
M1	451 (15)	19 (3)	8 (4)	
2010 TNM stage groupings (N = 3732)				< 0.001
I	1424 (47)	403 (73)	89 (49)	
II	390 (13)	74 (13)	63 (35)	
III	709 (24)	55 (10)	18 (10)	
IV	476 (16)	21 (4)	10 (6)	

TABLE 2. Cancer-specific Survival (CSS) Rates at 10 Years After Surgery by the Combinations of the ISUP Grading system, Coagulative Tumor Necrosis, and Sarcomatoid/Rhabdoid Differentiation for 3017 Patients With Clear Cell RCC

Group	ISUP Grade	Necrosis	Sarcomatoid/ Rhabdoid	N (%)	CSS (95% CI; No. at Risk)
1	1	No	No	272 (9.0)	89 (84-93; 123)
1	1	Yes	No	1 (< 0.1)	NA
2	2	No	No	1203 (39.9)	85 (83-88; 509)
3	2	Yes	No	53 (1.8)	67 (54-82; 27)
4	3	No	No	621 (20.6)	62 (58-67; 150)
5	3	Yes	No	587 (19.5)	30 (27-35; 93)
6	4	No	No	12 (0.4)	19 (6-66; 1)
7	4	Yes	No	103 (3.4)	24 (16-35; 9)
8	4	No	Yes	12 (0.4)	31 (13-75; 3)
9	4	Yes	Yes	154 (5.1)	8 (4-15; 4)

NA indicates not applicable.

TABLE 3. Cancer-specific Survival (CSS) Rates at 10 Years After Surgery by the Proposed Grading System and the ISUP Grading System for 3017 Patients With Clear Cell RCC

	N	CSS (95% CI; No. at Risk)	*P**	*c* index
Proposed grade				
Groups 1/2	1475	86 (84-88; 632)	Reference	0.764
Groups 3/4	674	62 (58-67; 177)	< 0.001	
Groups 5/6	599	30 (26-35; 94)	< 0.001	
Groups 7/8/9	269	15 (11-21; 16)	< 0.001	
ISUP grade				
1	272	89 (85-93; 123)	Reference	0.737
2	1256	84 (82-87; 536)	0.041	
3	1208	46 (43-50; 243)	< 0.001	
4	281	15 (11-20; 17)	< 0.001	

**P*-values represent comparisons of CSS between the grade listed and the reference group (ie, proposed groups 1/2 or ISUP grade 1).

RESULTS

Patient Selection

Slides were retrieved from the Mayo Clinic Tumor Registry. The mean number of slides reviewed per tumor was 3.1 (SD 2.9; range, 1 to 43). There was a significant increase in the number of slides reviewed per case from 1970 to 2006. This reflects a change in practice at the Mayo Clinic. In the 1970s multiple tissue sections were taken for frozen section analysis, and only a limited number of corresponding sections representative of the highest grade and stage were processed for permanent sections. Despite this change in practice, the proportion of cases with necrosis did not change significantly over time. For example, 26% of patients treated in 1970 had necrosis in contrast to 29% of patients treated in 2006.

During 1970 to 2006, none of the 3275 patients with M0 disease received preoperative systemic treatment. Nine received immediate postoperative radiation, and 1 was treated postoperatively with sorafenib for locally advanced disease. Thirteen (< 1%) underwent preoperative angioembolization; 4 of these patients had tumors with coagulative tumor necrosis (31%) compared with 867 (27%) of the patients without angioembolization ($P = 0.73$). In addition, the necrosis associated with embolization was of the infarct type in contrast to coagulative tumor necrosis as assessed for the current study. Of the 478 patients with M1 disease, 32 were treated preoperatively with radiation for their metastases, 7 received hormone therapy, 14 received immunotherapy, and 7 received chemotherapy; no patient was treated preoperatively with targeted therapy for their metastases. There were no statistically significant associations between preoperative treatment for metastases and the presence or absence of necrosis. Excluding patients receiving preoperative treatment did not significantly alter the study results.

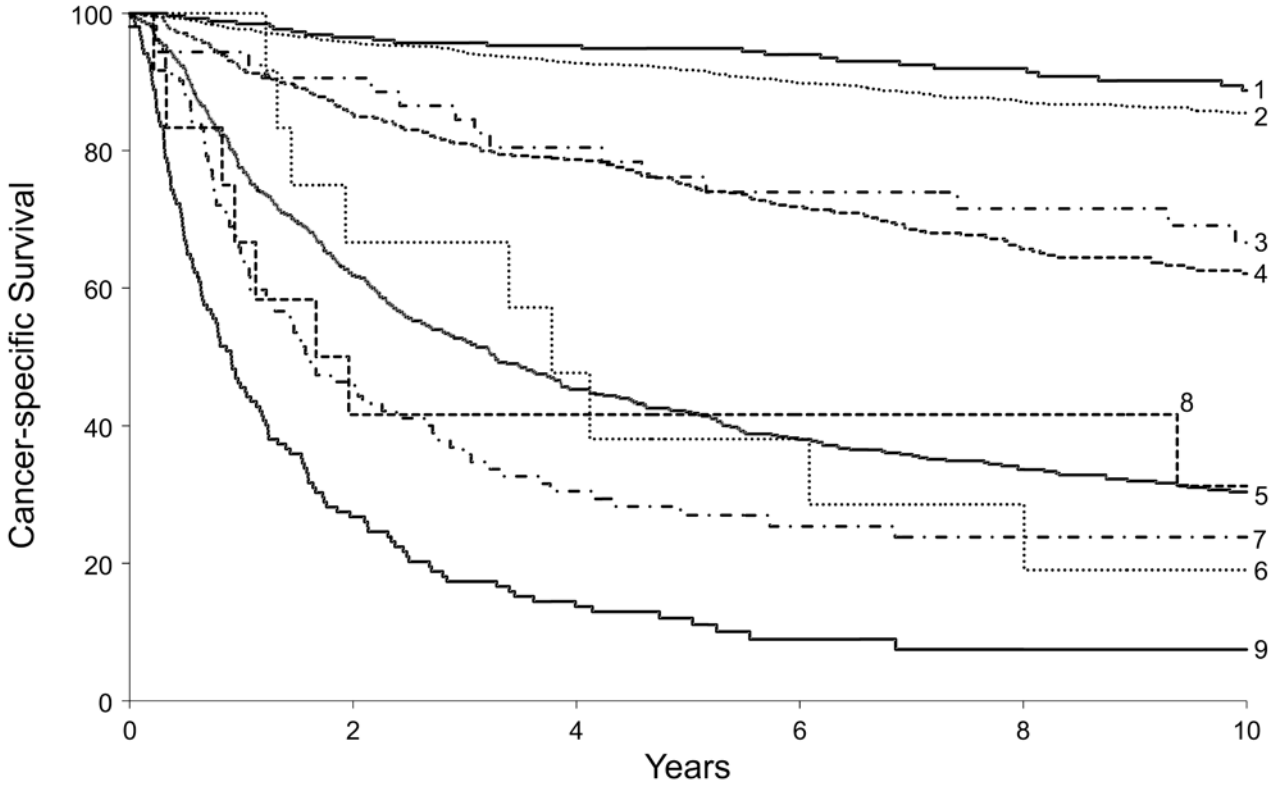

FIGURE 1. Cancer-specific survival by the combinations of the ISUP grading system, coagulative tumor necrosis, and sarcomatoid/rhabdoid differentiation for 3017 patients with clear cell RCC.

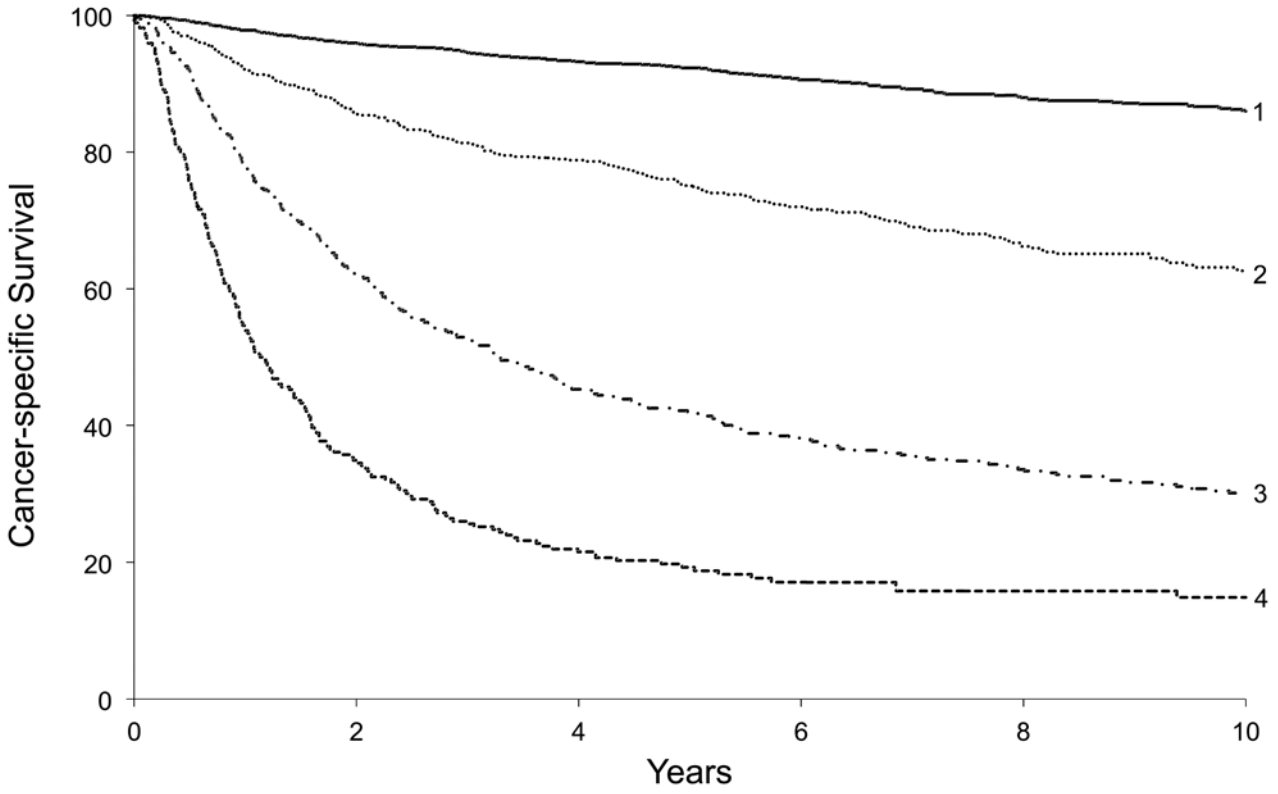

FIGURE 2. Cancer-specific survival by the proposed grading system for 3017 patients with clear cell RCC.

All Subtypes

There were 3017 (80%) patients with clear cell RCC, 556 (15%) with papillary RCC, and 180 (5%) with chromophobe RCC. Of the 3017 patients with clear cell RCC, 1996 died, including 1083 who died from RCC at a mean of 3.9 years after surgery (median 2.0 y; range, 0 to 31 y). The mean duration of follow-up for the 1021 patients who were still alive at last follow-up was 10.9 years (median 8.9 y; range, 0 to 40 y). Estimated cancer-specific survival rates (95% CI; number still at risk) at 5, 10, 15, and 20 years after surgery were 72% (70-74; 1773), 63% (61-65; 919), 57% (55-59; 456), and 43% (51-56; 227), respectively.

Of the 556 patients with papillary RCC, 297 died, including 67 who died from RCC at a mean of 3.6 years after surgery (median 2.4 y; range, 0 to 17 y). The mean duration of follow-up for the 259 patients who were still alive at last follow-up was 10.9 years (median 9.7 y; range, 0 to 32 y). Estimated cancer-specific survival rates (95% CI; number still at risk) at 5, 10, 15, and 20 years after surgery were 91% (88-93; 398), 86% (83-90; 220), 86% (82-89; 109), and 84% (79-88; 36), respectively.

Of the 180 patients with chromophobe RCC, 79 died, including 23 who died from RCC at a mean of 3.0 years after surgery (median 1.3 y; range, 0 to 16 y). The mean duration of follow-up for the 101 patients who were still alive at last follow-up was 10.9 years (median 8.5 y; range, 0 to 40 y). Estimated cancer-specific survival rates (95% CI; number still at risk) at 5, 10, 15, and 20 years after surgery were 89% (84-94; 123), 87% (81-92; 65), 85% (79-91; 41), and 82% (75-91; 21), respectively.

Cancer-specific survival was statistically significantly different between patients with clear cell RCC and those with papillary RCC ($P < 0.001$) and between patients with clear cell RCC and those with chromophobe RCC ($P < 0.001$) but not between patients with papillary and those with chromophobe RCC ($P = 0.71$).

Comparisons of the pathologic features of the ISUP grading system, coagulative tumor necrosis, sarcomatoid/rhabdoid differentiation, 2010 primary tumor classification, 2010 regional lymph node involvement, distant metastasis at nephrectomy, and the 2010 TNM stage groupings by RCC histologic subtype are shown in Table 1. These features varied greatly among the subtypes. For example, the proportions of tumors classified as grade 2 were 42%, 59%, and 81% for patients with clear cell, papillary, and chromophobe RCC, respectively ($P < 0.001$). Patients with papillary RCC were significantly more likely to have necrotic tumors (43%) compared with patients with clear cell (30%) and chromophobe (18%) RCC ($P < 0.001$). Chromophobe RCC tumors were more likely to have sarcomatoid/rhabdoid differentiation (8%) compared with clear cell (5%) and papillary (2%) RCC ($P < 0.001$).

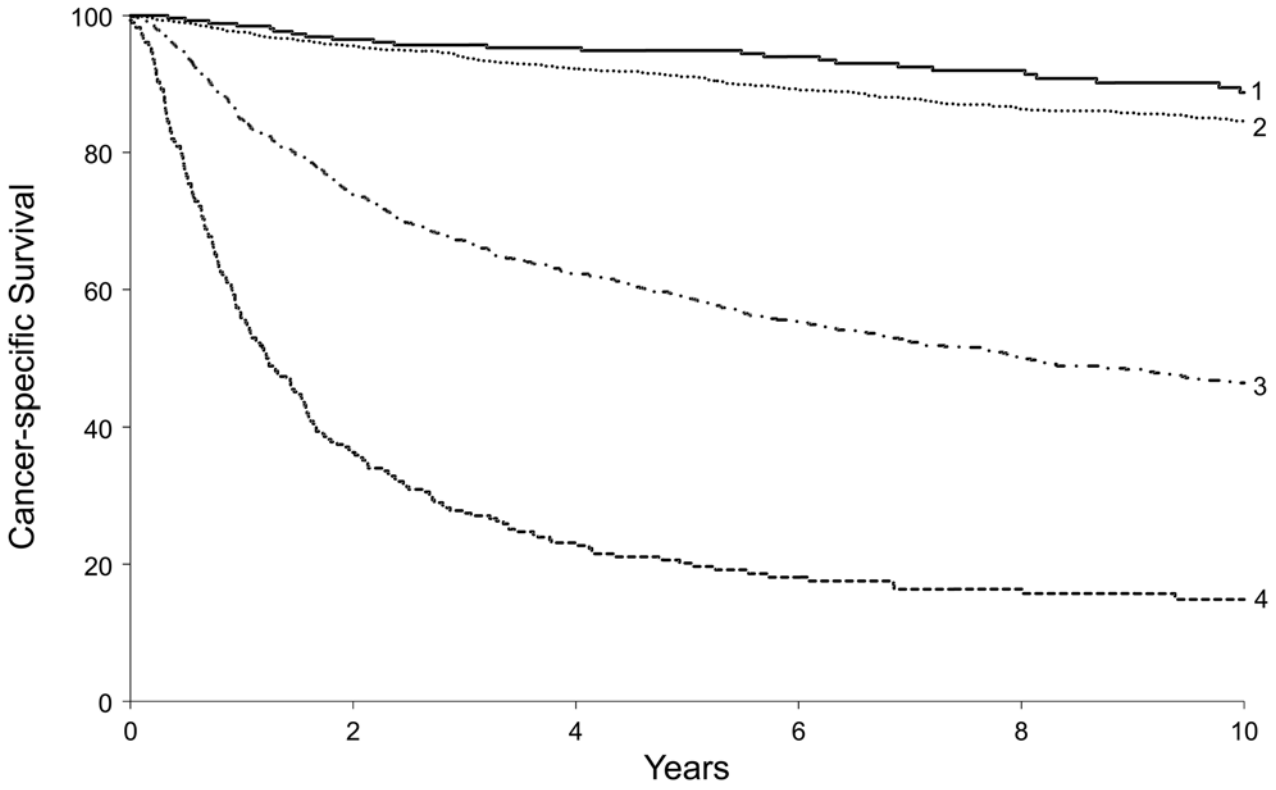

FIGURE 3. Cancer-specific survival by the ISUP grading system for 3017 patients with clear cell RCC.

Clear Cell RCC

The combinations of the ISUP grading system, coagulative tumor necrosis, and sarcomatoid/rhabdoid differentiation for the 3017 patients with clear cell RCC are summarized in Table 2. There was no statistically significant difference in cancer-specific survival between patients with ISUP grade 1 tumors and patients with non-necrotic grade 2 tumors (group 1 vs. 2; $P = 0.07$) or between patients with necrotic grade 2 tumors and patients with non-necrotic grade 3 tumors (group 3 vs. 4; $P = 0.34$). However, there was a statistically significant difference between patients with non-necrotic and those with necrotic grade 2 tumors (group 2 vs. 3; $P = 0.005$). Cancer-specific survival was similar for patients with necrotic grade 3 tumors and patients with non-necrotic, non-sarcomatoid/rhabdoid grade 4 tumors (group 5 vs. 6; $P = 0.69$). Cancer-specific survival was the poorest for patients with necrotic and sarcomatoid/rhabdoid grade 4 tumors (group 9). Survival for patients in this group was statistically significantly different compared with patients with necrotic, non-sarcomatoid/rhabdoid grade 4 tumors (group 9 vs. 7; $P < 0.001$) and those with non-necrotic, sarcomatoid/rhabdoid grade 4 tumors (group 9 vs. 8; $P = 0.032$).

These results were used to propose a novel 4-tiered grading classification for clear cell RCC consisting of groups 1/2, 3/4, 5/6, and 7/8/9. This proposed classification separates patients into those with grade 1 or non-necrotic grade 2 tumors; those with necrotic grade 2 or non-necrotic grade 3 tumors; those with necrotic grade 3 or non-necrotic, non-sarcomatoid/rhabdoid grade 4 tumors; and those with grade 4 tumors with either necrosis and/or sarcomatoid/rhabdoid differentiation. Cancer-specific survival for this proposed grading classification, as well as for the ISUP grading classification, is summarized in Table 3 and illustrated in Figures 1–3. Cancer-specific survival was statistically significantly different between patients in groups 1/2 and patients in groups 3/4 ($P < 0.001$), between patients in groups 3/4 and patients in groups 5/6 ($P < 0.001$), and between patients in groups 5/6 and patients in groups 7/8/9 ($P < 0.001$). Cancer-specific survival was also statistically significantly different between patients with ISUP grade 1 and those with ISUP grade 2 tumors ($P = 0.041$), between patients with ISUP grade 2 and those with ISUP grade 3 tumors ($P < 0.001$), and between patients with ISUP grade 3 and those with ISUP grade 4 tumors ($P < 0.001$). However, as demonstrated by the *c* indexes, the proposed grading classification contained greater predictive ability compared with the ISUP grading system (*c* indexes of 0.764 and 0.737, respectively). Cancer-specific survival for the proposed grading classification by the 2010 TNM stage groupings is summarized in Table 4 and illustrated in Figures 4–7. The proposed grading classification contained greater predictive ability compared with the ISUP

TABLE 4. Cancer-specific Survival (CSS) Rates at 10 Years After Surgery by Proposed Grading System and ISUP Grading System by the 2010 TNM Stage Groupings for 2999 Patients With Clear Cell RCC

Stage	N	CSS (95% CI; No. at Risk)	P*	c Index
TNM1				
Proposed grade				
Groups 1/2	1059	95 (93-96; 466)	Reference	0.717
Groups 3/4	265	83 (77-90; 72)	< 0.001	
Groups 5/6	83	64 (53-78; 24)	< 0.001	
Groups 7/8/9	17	40 (22-72; 6)	< 0.001	
ISUP grade				
1	208	95 (91-98; 100)	Reference	0.699
2	872	94 (92-96; 380)	0.41	
3	327	78 (72-84; 82)	< 0.001	
4	17	40 (22-72; 6)	< 0.001	
TNM II				
Proposed grade				
Groups 1/2	168	82 (75-88; 88)	Reference	0.667
Groups 3/4	115	73 (64-82; 40)	0.33	
Groups 5/6	90	48 (38-61; 27)	< 0.001	
Groups 7/8/9	17	19 (6-58; 1)	< 0.001	
ISUP grade				
1	28	82 (67-100; 11)	Reference	0.638
2	153	81 (74-88; 83)	0.91	
3	190	61 (53-69; 60)	0.10	
4	19	27 (11-63; 2)	< 0.001	
TNM III				
Proposed grade				
Groups 1/2	164	70 (62-78; 62)	Reference	0.682
Groups 3/4	188	56 (48-65; 55)	0.10	
Groups 5/6	253	29 (23-36; 36)	< 0.001	
Groups 7/8/9	104	24 (16-35; 9)	< 0.001	
ISUP grade				
1	21	86 (69-100; 9)	Reference	0.641
2	153	66 (59-76; 58)	0.67	
3	425	40 (35-46; 86)	0.017	
4	110	22 (15-34; 9)	< 0.001	
TNM IV				
Proposed grade				
Groups 1/2	74	15 (9-26; 9)	Reference	0.585
Groups 3/4	101	12 (7-22; 7)	0.94	
Groups 5/6	170	7 (4-12; 6)	0.023	
Groups 7/8/9	131	NAR	< 0.001	
ISUP grade				
1	10	NAR	Reference	0.571
2	71	16 (9-28; 9)	0.21	
3	260	9 (6-14; 13)	0.56	
4	135	NAR	0.35	

*P-values represent comparisons of CSS between the grade listed and the reference group (ie, proposed groups 1/2 or ISUP grade 1).
NAR indicates no patients left at risk.

grading classification for 2010 TNM stage groupings I, II, III, and IV.

The importance of necrosis in predicting cancer-specific survival can be further illustrated by adding necrosis to the ISUP grading classification in the Cox model. In this model necrosis added statistically significant information to predict death (hazard ratio 2.40; $P < 0.001$).

Papillary RCC

The combinations of the ISUP grading system, coagulative tumor necrosis, and sarcomatoid/rhabdoid differentiation for the 556 patients with papillary RCC are summarized in Table 5. Three patients with necrotic grade 1 tumors were combined with 8 patients with non-necrotic grade 1 tumors to form group 1. There were no patients with non-necrotic, non-sarcomatoid/rhabdoid grade 4 tumors (group 6). As there were only 3 patients with necrotic, non-sarcomatoid/rhabdoid grade 4 tumors (group 7) and only 1 patient with non-necrotic, sarcomatoid/rhabdoid grade 4 tumors (group 8), these patients were combined for analysis. Cancer-specific survival by these combinations are summarized in Table 5 and illustrated in Figure 8. Necrosis did not add statistically significant information to predict death from RCC when added to the ISUP grading system in a Cox model (hazard ratio 1.23; $P = 0.41$).

Chromophobe RCC

The combinations of the ISUP grading system, coagulative tumor necrosis, and sarcomatoid/rhabdoid differentiation for the 180 patients with chromophobe RCC are summarized in Table 6. There were no patients with grade 1 tumors (group 1), no patients with non-necrotic, non-sarcomatoid/rhabdoid grade 4 tumors (group 6), and no patients with necrotic, non-sarcomatoid/rhabdoid grade 4 tumors (group 7). As there was only 1 patient with a non-necrotic, sarcomatoid/rhabdoid grade 4 tumor (group 8), this patient was combined with group 9 for analysis. Cancer-specific survival by these combinations are summarized in Table 6 and illustrated in Figure 9. As with papillary RCC, necrosis did not add statistically significant information to predict death from RCC when added to the ISUP grading system in a Cox model (hazard ratio 1.53; $P = 0.52$).

DISCUSSION

In this study we have investigated the prognostic significance of the ISUP grading system, utilizing separate series of cases of the 3 most common subtypes of RCC. We have also assessed the prognostic significance of microscopic coagulative tumor necrosis as an additional grading parameter.

We found that coagulative tumor necrosis, when incorporated into the ISUP grading system for clear cell RCC, provided greater predictive ability for cancer-specific survival than the ISUP grading system alone. The effect of incorporating necrosis into a grading system was most profound in ISUP grade 3 tumors. The 10-year cancer-specific survival rate for patients with grade 3 tumors without necrosis was 62% compared with 30% in patients with grade 3 tumors that contained necrosis. The result of incorporating necrosis into the grading system is the creation of 4 groups that differ significantly in cancer-specific survival outcomes. Moreover, within TNM stage groupings, the grading system that incorporated necrosis maintained its superior predictive power over the ISUP grading system. This provides a greater refinement of the

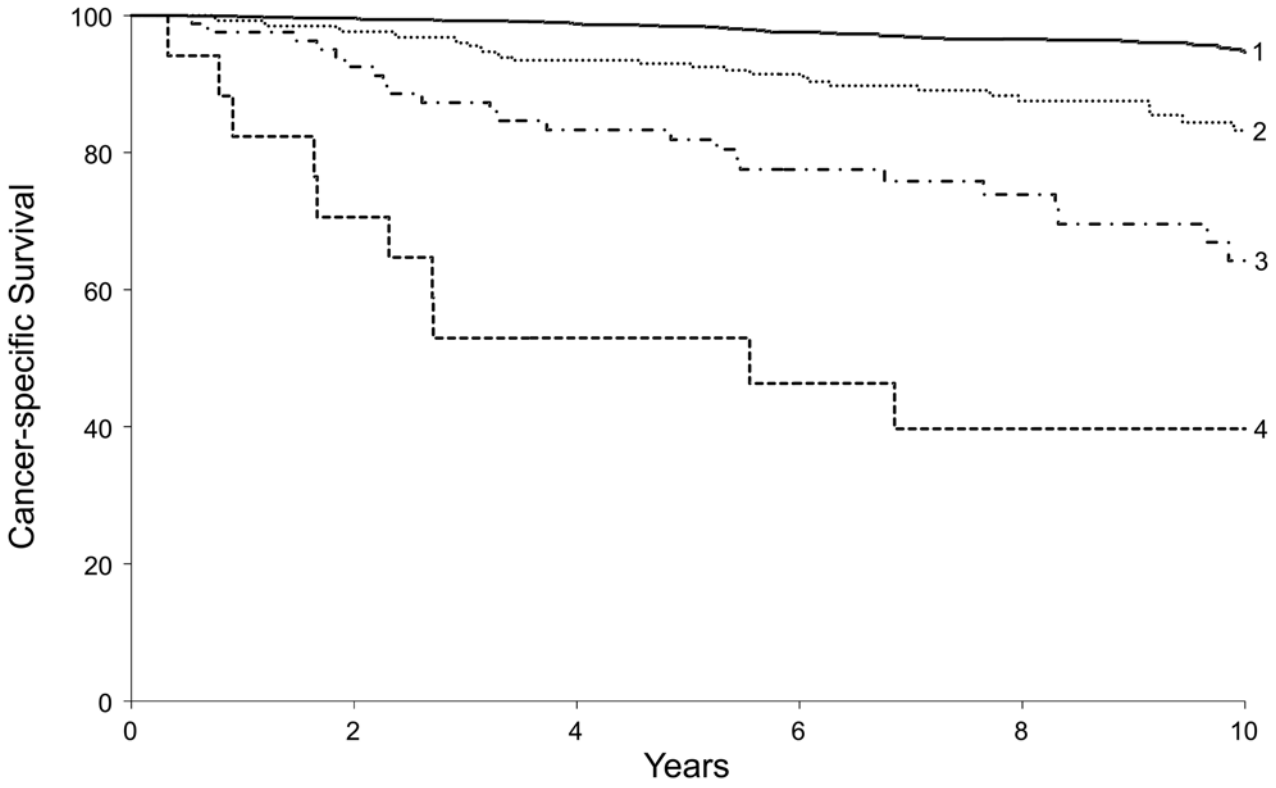

FIGURE 4. Cancer-specific survival by the proposed grading system for 1424 patients with TNM stage I clear cell RCC.

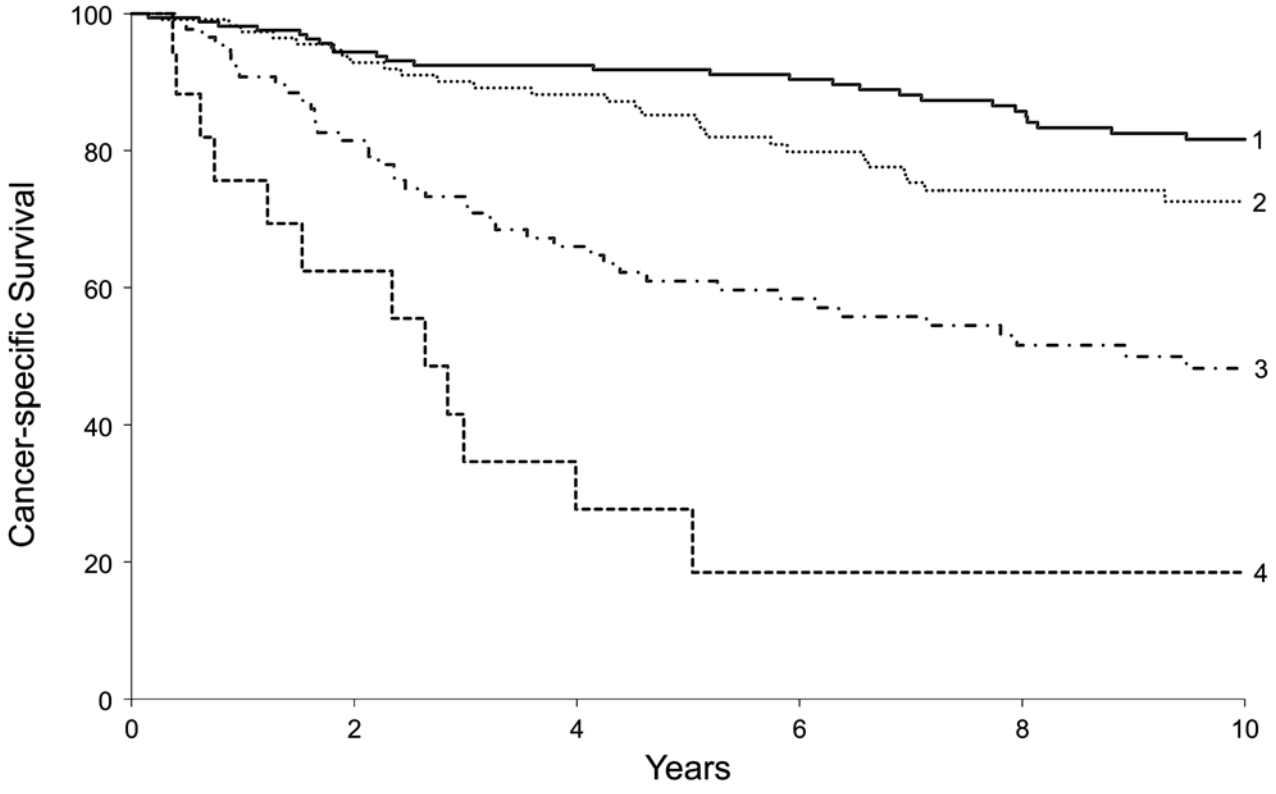

FIGURE 5. Cancer-specific survival by the proposed grading system for 390 patients with TNM stage II clear cell RCC.

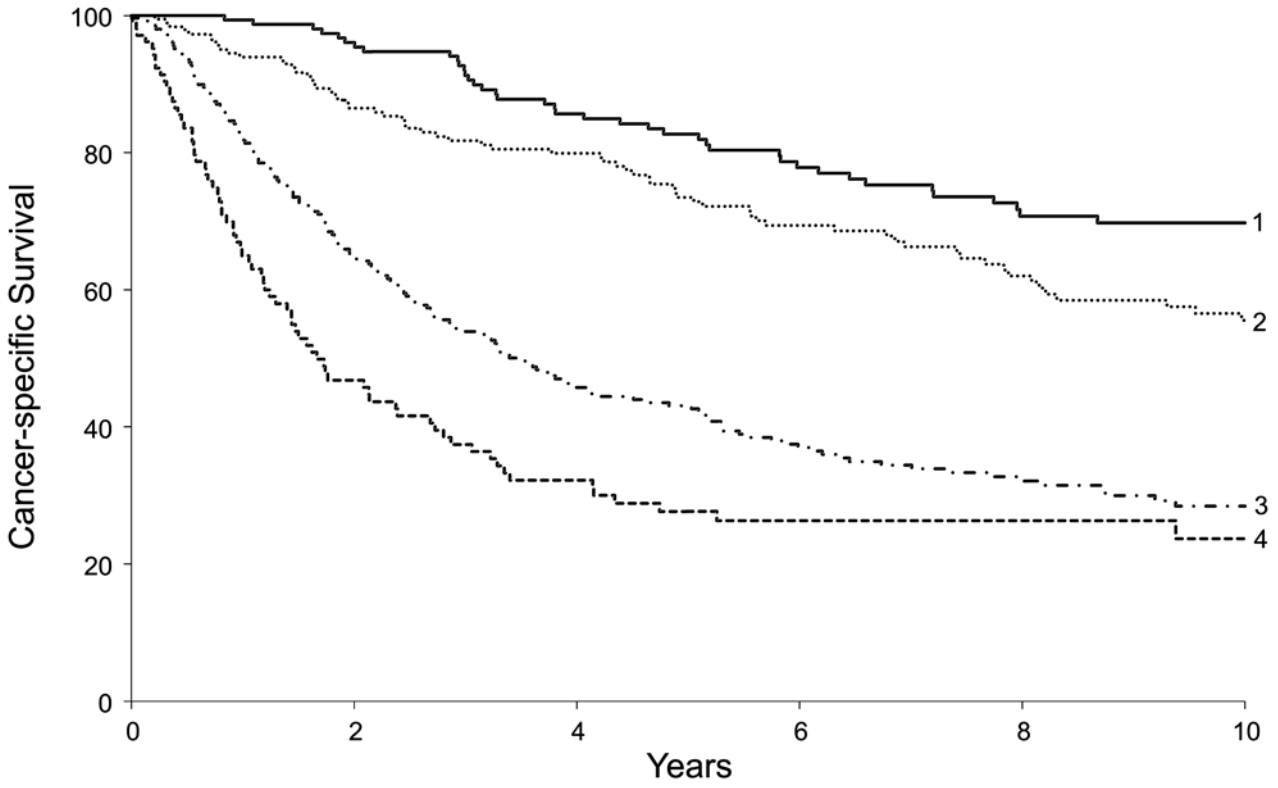

FIGURE 6. Cancer-specific by the proposed grading system for 709 patients with TNM stage III clear cell RCC.

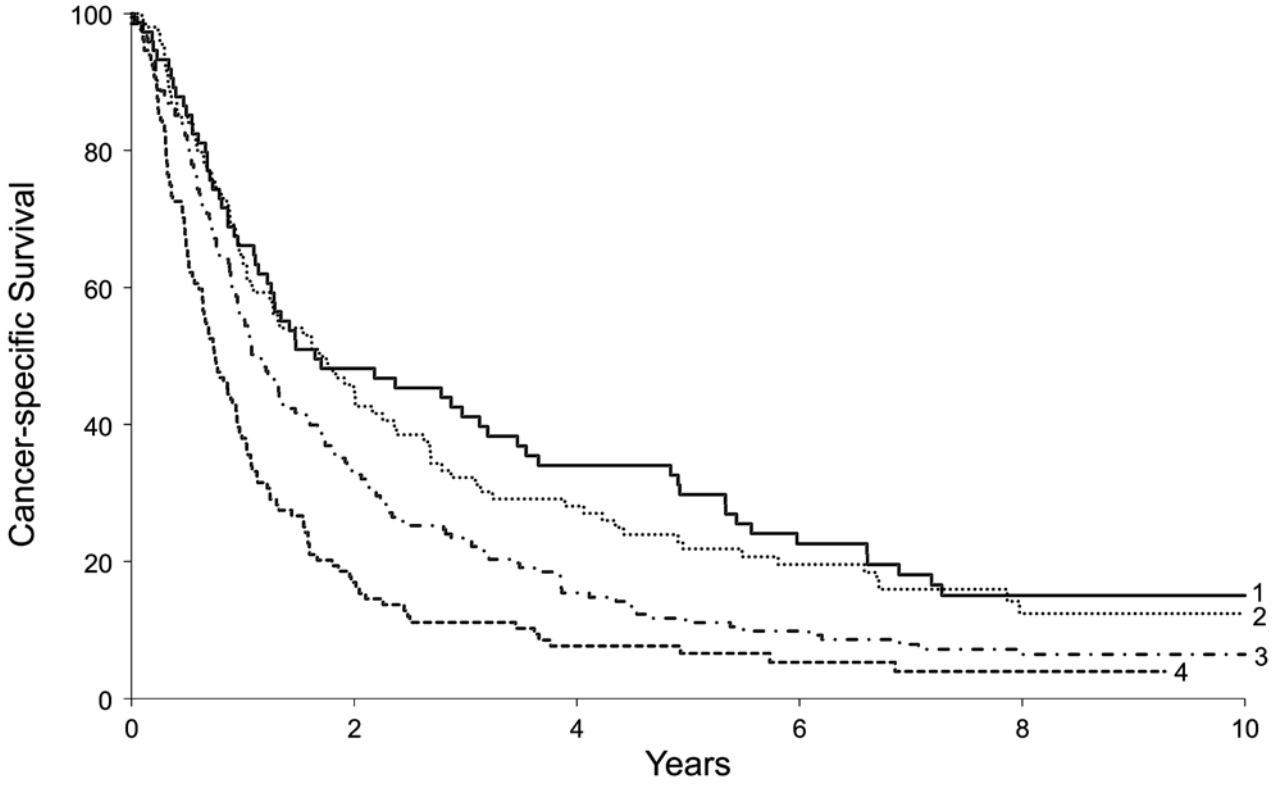

FIGURE 7. Cancer-specific survival by the proposed grading system for 476 patients with TNM stage IV clear cell RCC.

TABLE 5. Cancer-specific Survival (CSS) Rates at 10 Years After Surgery by the Combinations of the ISUP Grading System, Coagulative Tumor Necrosis, and Sarcomatoid/Rhabdoid Differentiation for 556 Patients With Papillary RCC

Group	ISUP Grade	Necrosis	Sarcomatoid/ Rhabdoid	N (%)	CSS (95% CI; No. at Risk)
1	1	No/yes	No	11 (2.0)	100 (100-100; 5)
2	2	No	No	215 (38.7)	94 (90-97; 90)
3	2	Yes	No	112 (20.1)	94 (89-99; 54)
4	3	No	No	91 (16.4)	80 (71-89; 33)
5	3	Yes	No	114 (20.5)	75 (67-84; 36)
6	4	No	No	0 (0)	NA
7/8	4	No/yes	No/yes	4 (0.7)	50 (19-100; 1)
9	4	Yes	Yes	9 (1.6)	25 (8-83; 1)

NA indicates not applicable.

current ISUP grading system. Most importantly, incorporating necrosis into a grading system with greater predictive power in determining outcome puts the significance of tumor necrosis into clinical context rather than simply reporting the presence or absence of necrosis. As discovered at the recent consensus conference in Vancouver, up to 30% of urologic pathologists do not report on the presence or absence of necrosis, and we believe that this is likely to be higher among general pathologists. In addition, of several nomograms in use in clinical practice, only 1 includes coagulative necrosis as a prognostic variable. For these reasons, we believe it important for a grading system for clear cell to include coagulative necrosis. We do not believe that this adds to the complexity of grading renal tumors unduly, but rather indicates refinement of grading on the basis of our accumulated knowledge of RCC subtypes. Our study found that the incorporation of tumor necrosis into grading systems for papillary and chromophobe RCC did not have the same effect of improving the predictive ability of the grading system as seen in clear cell RCC.

In studies that have investigated the significance of tumor necrosis, microscopic necrosis has been correlated with outcome, independent of tumor grade, tumor size, and TNM stage for clear cell RCC.[9,13,15,16] Interestingly, microscopic tumor necrosis has also been shown to predict outcome for clear cell RCC, independent of cell cycle activity as determined by Ki-67 immunohistochemistry, indicating that necrosis is not solely a marker of high tumor proliferation or growth.[18] In one of our institutions, we have incorporated the presence of necrosis into an algorithm, the SSIGN score, used clinically in the management of patients with clear cell RCC.[19] This algorithm, along with the importance of tumor necrosis in predicting outcome, has been validated by multiple institutions.[13,20–22] These studies have defined necrosis on the basis of microscopic rather than macroscopic findings and used specific features to separate necrosis from other degenerative changes frequently associated with these

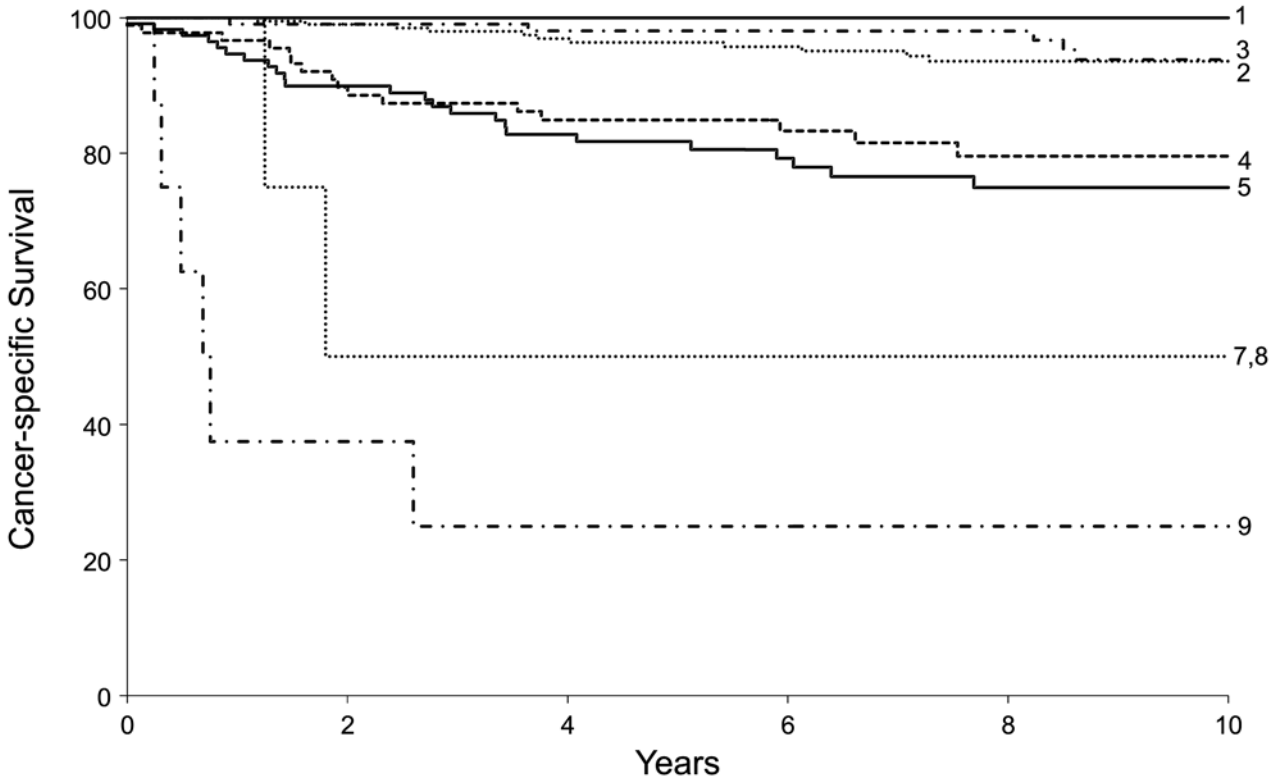

FIGURE 8. Cancer-specific survival by the combinations of the ISUP grading system, coagulative tumor necrosis, and sarcomatoid/rhabdoid differentiation for 556 patients with papillary RCC.

TABLE 6. Cancer-specific Survival (CSS) Rates at 10 Years After Surgery by the Combinations of the ISUP Grading System, Coagulative Tumor Necrosis, and Sarcomatoid/Rhabdoid Differentiation for 180 Patients With Chromophobe RCC

Group	ISUP Grade	Necrosis	Sarcomatoid/ Rhabdoid	N (%)	CSS (95% CI; No. at Risk)
1	1	No/yes	No	0 (0)	NA
2	2	No	No	131 (72.8)	93 (88-98; 52)
3	2	Yes	No	14 (7.8)	86 (69-100; 5)
4	3	No	No	15 (8.3)	93 (82-100; 6)
5	3	Yes	No	6 (3.3)	80 (52-100; 1)
6	4	No	No	0 (0)	NA
7	4	Yes	No	0 (0)	NA
8/9	4	No/yes	Yes	14 (7.8)	25 (9-65; 1)

NA indicates not applicable.

tumors, particularly low-grade tumors, that can be confused with coagulative tumor necrosis. In particular foci of fibrosis, hyalinization, and hemorrhage are not considered indicative of necrosis. It is critical that coagulative necrosis is appropriately defined and assessed in clear cell RCC. In our study, tumor necrosis occurred in only a single ISUP grade 1 clear cell RCC and in only 4.2% of ISUP grade 2 tumors. In contrast, a study by Klatte et al[23] of 343 reviewed pathology cases of clear cell RCC reported coagulative tumor necrosis in nearly 50% of grade 1 and 2 tumors, and, perhaps not surprisingly, they reported no significant association of necrosis and outcome in a multivariable model. These differences suggest that tumor necrosis is not being assessed similarly in all institutions, and utilization of any grading system incorporating necrosis requires accepted reproducible criteria for the identification of coagulative tumor necrosis. Studies that have independently validated the SSIGN score indicate that such criteria have been established and are reproducible.

Although tumor necrosis is reported to occur with relative frequency in RCC, the mechanism remains unclear, and it has been suggested that this occurs as tumors outgrow their own blood supply.[16] Against this suggestion is the observation that necrosis is seen in small clear cell RCCs. It has been demonstrated that in clear cell RCC the microvessel density decreases as tumors increase in size, with vascular remodeling resulting in the development of larger-diameter vascular channels.[24] It is possible that this may result in focal necrosis, as vascular channels lose their patency during the remodeling process. Tumor necrosis is more frequently seen in papillary RCC than in other subtypes of RCC,[16] and this may be a reflection of the complex architecture of the tumor, with papillary cores consisting of small vessels supported by loose connective tissue. It is possible that this complex

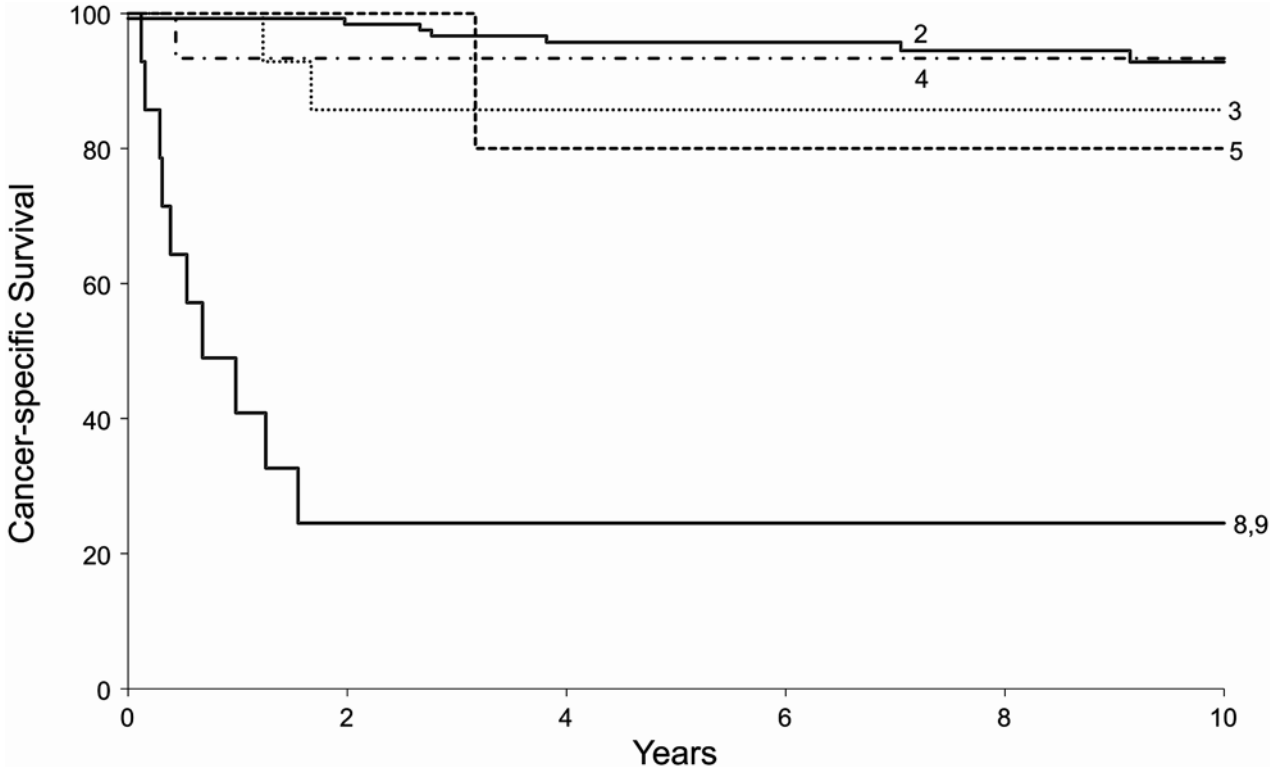

FIGURE 9. Cancer-specific survival by the combinations of the ISUP grading system, coagulative tumor necrosis, and sarcomatoid/rhabdoid differentiation for 180 patients with chromophobe RCC.

architecture may promote the development of necrosis due to papillary malformation, epithelial overgrowth, or increased susceptibility to trauma.

Analysis of grading for both clear cell and papillary RCCs showed a similar outcome for ISUP grade 1 and 2 tumors, although the presence of prominent nucleoli (ISUP grade 3) was associated with significantly poorer survival. Stratification of cases of papillary RCC in our series, according to the degree of nucleolar prominence and the presence or absence of tumor necrosis, failed to provide prognostic information superior to that derived from ISUP grading alone. This is likely a reflection of the predisposition of papillary cell RCC to undergo spontaneous tumor necrosis that appears to be unrelated to tumor outcome.[15,16]

Tumor necrosis is less frequently observed in chromophobe RCC; however, previous studies have shown necrosis to be of prognostic significance on univariate analysis.[16] The combination of the ISUP grading system and the presence or absence of tumor necrosis in our series failed to provide significant prognostic information. The major contributing factor to the failure of our proposed grading system to adequately stratify cases according to outcome is most likely the weak predictive power of nucleolar prominence for this tumor type, as has been previously noted.[2,9,23] To address this, a novel form of grading chromophobe RCC on the of nuclear pleomorphism, nuclear crowding, and sarcomatoid differentiation has been proposed.[25] From our results and those of other series it would appear, however, that the development of sarcomatoid differentiation and TNM stage are the only independent prognostic markers for this morphotype of RCC.[26,27]

The Fuhrman grading system was validated utilizing a combined series of tumor subtypes, including a surprising number of tumors described as showing a mixed clear cell and papillary RCC morphology.[3] In the 30 years since the publication of this study, enormous advances have been made in the identification and validation of many variable types of renal epithelial neoplasia, each having a unique morphology, genetic constitution, and clinical behavior.[9,28,29] Just as it is now considered inappropriate to characterize all these tumors simply as RCC, we believe that it is equally inappropriate that a uniform grading system should be applied to all renal epithelial tumors. In this study we have defined a novel grading system applicable to clear cell RCC, that would appear to be prognostically superior to the ISUP grading system. We have also shown that this novel system is not applicable to papillary RCC and have further validated the ISUP recommendation that chromophobe RCC not be graded.[7,30]

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