Extensive Necrosis in Renal Cell Carcinoma Specimens: Potential Clinical and Prognostic Implications

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Abstract

Background: Extensive necrosis is rare in primary renal cell carcinoma. This finding may reflect the biological characteristics of the carcinoma and therefore could be of prognostic and clinical value.

Objectives: To assess the incidence of necrosis in renal cell carcinoma and its potential prognostic value.

Methods: We conducted a consecutive retrospective study of 173 patients after radical nephrectomy for renal cell carcinoma. Clinical and pathological data were collected from hospital medical records and compiled into a computerized database.

Results: Extensive necrosis was found in 31 tumor specimens (17.9%). Univariate analysis showed that the specimens with extensive necrosis were significantly larger and manifested more perirenal and venous extension than the tumors without necrosis. The size of the renal tumor was the only parameter that remained significant in multivariate analysis ($P = 0.0001$). Overall disease-free survival did not differ significantly between patients with necrotic tumors and those without (68% and 66% respectively).

Conclusions: The finding of extensive necrosis in renal cell carcinoma specimens does not seem to be related to tumor biology but rather may reflect the relation between size and vascularity of the tumor.

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Tumor stage is recognized as the single most significant prognostic parameter for renal cell carcinomas. Morphologically based complementary classification systems have been proposed to stratify renal cell carcinomas into prognostic subgroups, without offering applicable independent and meaningful prognostic information [1]. Renal cell carcinomas are noted for the variability of their histopathological appearance. Tumors differ morphologically, manifesting distinctive types of cells and patterns of growth. These morphologically defined subtypes are known to comprise distinct prognostic subgroups. The amount of necrosis found in renal tumor specimens also varies greatly. Conventional renal cancers usually manifest focal patchy necrosis; certain pathologic subtypes are characterized by massive necrosis that is absent in others [1]. This variability may correlate with prognosis.

In other cancers, there are data to support the correlation between prognosis and the presence or absence of tumor necrosis. In astrocytic neoplasms, the presence of necrosis characterizes the most anaplastic form – the glioblastoma multiforme – and is significantly associated with a worse outcome [2]. In deep-seated soft tissue sarcomas the absence of necrosis is a favorable prognostic sign. In a study by Gustafson et al. [3], approximately 46% of the patients who had evidence of necrosis developed metastasis, compared to none of the patients who had tumors without necrosis. In smooth muscle tumors arising in the gastrointestinal tract and retroperitoneum, tumor necrosis is closely associated with aggressive behavior even when mitoses are infrequent, while it is doubtful that benign smooth muscle tumors develop extensive tumor cell necrosis [4]. In addition, the classification of uterine smooth muscle neoplasms was recently shifted from exclusive reliance upon a mitotic index to integration of additional histopathologic characteristics including the presence or absence of tumor necrosis [5].

These data suggest that the presence of necrosis could possibly reflect the biological characteristics of primary renal cell carcinoma and are thus of clinical and prognostic value. The purpose of this study was to assess the incidence of extensive necrosis in renal cell carcinoma specimens and to characterize its potential clinical and prognostic implications.

Patients and Methods

We conducted a retrospective study of a consecutive series of 173 patients with renal tumors. They comprised 98 men and 75 women whose mean age was 65.5 years (range 21–92). Mean follow-up was 49 months (range 3–108 months). Ninety tumors (52%) originated on the left side and 83 on the right side (48%). The mean tumor diameter was 5.5 cm (range 0.5–22 cm).

The diagnosis of renal cell carcinoma was histologically confirmed in 164 patients. The remaining nine patients had benign tumors (oncocytomas). Tumors were classified according to the recent morphologic cytogenetic classification [6]. Conventional (clear cell) renal tumors comprised 85% of all renal tumors in this study, and papillary subtypes 7.5%. Four patients had unclassified tumors with a predominant sarcoma-

Table 1. Distribution of TNM classification of 173 renal cell tumors

TNM classification	Patients	%
T1	113	65.3
T2	20	11.6
T3A	16	9.2
T3B	16	9.2
T2N+	2	1.2
T3AN+	2	1.2
T3BN+	2	1.2
T1M+	1	0.6
T2M+	1	0.6
Total	173	100.0

toid component. Three of these four patients presented with advanced disease (two patients had lymph node metastasis, and one patient had caval involvement); the fourth patient had a large confined tumor. Nine patients (5.2%) had oncocytomas. All nine oncocytomas were smaller than 5.5 cm and were confined to the renal capsule. Due to their clinically benign course and uniform lack of necrosis, oncocytomas were excluded from survival analysis. Necrosis was defined as complete loss of visible nuclear chromatin material. The extent of necrosis was estimated visually from multiple sections taken from different sites in the tumor.

The TNM classification is based on the 1997 revision of the TNM staging of renal cell carcinomas [Table 1] [7]. Overall, 133 tumors (76.9%) were confined to the kidney, 113 tumors were 70 mm or smaller (T1), and 20 tumors were larger than 70 mm (T2). Perirenal extension was found in 16 patients (9.2%) and extension to the renal vein and/or inferior vena cava was seen in an additional 16 patients (9.2%). Regional lymph node metastasis was reported in six patients (3.6%) and distant metastasis was evident at presentation in two (1.2%).

Clinical and pathological data were collected from hospital medical records and compiled into a computerized database. Survival data were obtained from hospital medical records, records of the Ministry of National Internal Affairs, or telephonic confirmation of current status if information could not be derived from the former sources.

Statistical analysis was performed using the Pearson, chi-square and Student *t*-tests as needed. Survival analysis was performed using log rank and Cox's tests.

Results

Extensive necrosis was found in 31 tumor specimens (17.9%). Necrosis of the entire tumor was not encountered in this study and regions of viable tumor were apparent in all cases. Univariate analysis demonstrated that tumors manifesting necrosis were significantly larger than the tumors without necrosis. (7.9 and 5.5 cm respectively, Student *t*-test, $P = 0.0001$). Prominent necrosis was evident in 40% of the T2 tumors as compared to only 11.5% of the T1 tumors (Pearson, chi-square test, $P = 0.001$).

Eight of the 31 tumors with necrosis (25.8%) extended into the perirenal fat compared to only 17 of the 142 tumors without necrosis (12%) ($P = 0.04$). Renal vein or caval extension was more than twice as common in tumors with necrosis as in tumors without necrosis (19.4 and 8.5% respectively), however this trend was not statistically significant ($P = 0.07$).

Table 2. Necrosis in renal tumor specimens according to TNM classification

	Tumors without necrosis		Tumors with necrosis		Total
	Patients	%	Patients	%	
T1	100	88.5	13	11.5	113
T2	12	60.0	8	40.0	20
T3A	13	81.3	3	18.8	16
T3B	10	62.5	6	37.5	16
TX_N+	5	83.3	1	16.7	6
TX_M1	2	100.0	–	0.0	2
Total	142	82.1	31	17.9	173

TX = any T category

Table 3. Necrosis in renal tumor specimens according to pathologic subtypes

Classification of	Tumors without necrosis		Tumors with necrosis		Total
renal cell cancer	Patients	%	Patients	%	
Conventional	121	82.3	26	17.7	147
Papillary	10	76.9	3	23.1	13
Unclassified	2	50.0	2	50.0	4
Oncocytoma	9	100.0	–	0.0	9
Total	142	82.1	31	17.9	173

Overall, the incidence of necrosis in renal tumors confined to kidney (stages T1-T2, N0, M0) was 15.8% (21 of 133) compared to 25.0% (10 of 40) in tumors with perirenal extension and/or metastasis ($P = 0.21$). Pathological stage, lymph node involvement or distant metastasis was not correlated with the presence or absence of necrosis [Table 2].

Presence or absence of necrosis according to histologic tumor classification is presented in Table 3. The incidence of necrosis in papillary tumors was slightly higher than the incidence in conventional clear cell carcinomas. Necrosis was found in two of the four tumors with prominent sarcomatoid component. None of the nine oncocytomas manifested necrosis.

Size of the renal tumor was the only parameter that remained significant in multivariate analysis assessing the correlation between necrosis and the other clinicopathological parameters ($P = 0.0001$). Necrosis in the tumor specimen did not correlate with extension into the perirenal fat ($P = 0.39$), venous involvement ($P = 0.06$) or confinement to the kidney ($P = 0.48$). Overall, the disease-free survival rate did not differ significantly between patients with necrosis in the tumor specimen and patients without tumor necrosis (68% and 66% respectively).

Discussion

The significance of tumor necrosis as a prognostic parameter in renal cell carcinoma was briefly addressed in several early

studies with inconsistent conclusions. Fetter [8] suggested that necrosis and hemorrhage in renal cell carcinomas represent favorable tumor characteristics. Other researchers provided contradictory results connecting necrosis with metastatic disease [9] or decreased survival [8]. Yet, in still other series neither the presence of necrosis nor its extent influenced the outcome [10–14].

Absence of necrosis is characteristically associated with certain benign renal tumor subtypes, including cortical adenomas and oncocytomas. Additionally, necrosis is only rarely found in the favorable chromophobe cell variant of renal carcinomas. On the other hand, massive necrosis is a prominent feature of the favorable papillary renal cell carcinomas, while unfavorable collecting-duct carcinomas present as firm masses without hemorrhage or necrosis [1].

The absence of necrosis in unfavorable pathologic subtypes or its massive presence in favorable variants may be explained by the different vascularity of these tumors. Hence, the hypovascular papillary carcinoma is characterized by prominent necrosis despite its favorable clinical course. The relatively hypervascular conventional renal cell carcinomas usually manifest only patchy focal necrosis. However, when these tumors grow to larger sizes extensive necrosis may develop, indicating the probable importance of the ratio between size and vascularity. The independent effect of tumor vascularity has yet to be determined [15,16].

The incidence of extensive necrosis in the present study was 17.9% in comparison to 13% reported by Roosen et al. [16]. Univariate analysis indicated that advanced stage, larger tumors, extension into the perirenal fat and venous involvement were associated with increased incidence of necrosis, implying that necrosis may be associated with adverse prognosis. However, in multivariate analysis, size of the tumor was the only parameter that remained significant. Furthermore, overall and stage-adjusted survival did not differ significantly between patients with necrosis in the tumor specimen and patients without tumor necrosis. These results may be influenced by an inaccurate estimation of the extent of necrosis, which was done visually from multiple sections taken from different sites in the tumor and not from whole-mount step sections. Also, the mean follow-up period of 49 months may be relatively short for a tumor like renal cell carcinoma, which may recur later. Our results refute a recent work by Roosen et al. [16] who showed that the degree of necrosis (either less or more than 50%) significantly affected actuarial survival on both univariate and multivariate survival analyses. Nevertheless, their conclusion might be biased by the inclusion of oncocytomas, which are clinically benign and do not manifest necrosis, in the survival analysis. Additionally, these investigators did not include tumor stage, which was the most significant prognostic parameter in the multivariate analysis [17].

In conclusion, the finding of extensive necrosis in renal cell carcinoma specimens does not seem to be an independent prognostic factor but rather may reflect the relation between tumor size and vascularity.

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Weird clothing is de rigueur for teenagers, but today's generation of teens is finding it difficult to be sufficiently weird ... because the previous generation, who went through adolescence in the sixties and seventies, used up practically all the available weirdness.

P.J. O'Rourke, ***Modern Manners****, 1983*