

Prognostic Significance of Primary-Tumor Extension, Stage and Grade of Nuclear Differentiation in Patients with Renal Cell Carcinoma

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Surgery remains the preferred therapy for renal cell carcinoma. The various adjunctive or complementary therapies currently yield disappointing results. Identifying reliable prognostic factors could help in selecting patients most likely to benefit from postoperative adjuvant therapies.

We reviewed the surgical records of 78 patients who had undergone radical nephrectomy with lymphadenectomy for renal cell carcinoma, matched for type of operation and histology. According to staging (TNM), 5.1% of the patients were classified as stage I, 51.3% as stage II, 29.5% as stage III and 14.5% as stage IV. Of the 78 patients 40 were T₁N₀ and 21 T₁aN₀. Tumor grading showed that 39.7% of the patients had well-differentiated tumors (G₁), 41.1% moderately-differentiated (G₂), and 19.2% poorly-differentiated tumors (G₃).

Overall actuarial survival at 5 and 10 years was 100% for stage I; 91.3% at 5 years and 83.1% at 10 years for stage II; 45.5% and 34.1% for stage III; and 29.1% and nil for stage IV (stage II vs stage III $p = 0.0001$). Patients with tumors confined to the kidney (pT₁N₀) had better 5- and 10-year survival rates than patients with tumors infiltrating the perirenal fat (pT₂N₀) ($p = 0.000006$). Survival differed according to nuclear grading (G₁ vs G₃; $p = 0.000005$; G₁ vs G₂; $p = 0.0009$).

In conclusion our review identified tumor stage, primary-tumor extension, and the grade of nuclear differentiation as reliable prognostic factors in patients with renal cell carcinomas.

Key Words: Prognostic factors, Renal cell carcinoma

Surgery remains the only treatment for localized kidney carcinomas. Complementary or adjuvant therapies (chemotherapy, radiation, hormones and immunotherapy) seem of doubtful therapeutic benefit after radical surgery (R0). To identify patients who stand a chance of benefitting from adjuvant therapy, more information is needed on unfavorable prognostic factors.

The clinical and morphologic variables most closely related to survival are tumor diameter, the histopathological subtype, the grade of cellular differentiation (G), primary-tumor extension (T), lymph-node involvement, renal vein involvement, the metastatic site, tumor-cell DNA content (ploidy), cell nucleus morphometry and determination of the nuclear area. In this study we assessed the importance of primary-tumor extension and grade of differentiation as prognostic factors in patients who had undergone radical nephrectomy for renal carcinoma.

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Materials and Methods

From the case records of the 1st Department of General Surgery at the University of Rome, "La Sapienza", Italy, we selected a group of 78 patients (47 men, age range 16-83 years) who had undergone surgery for renal cell carcinoma from 1980 to 1998 and who had regular follow-up, similar operations and similar histopathological findings. In 39 patients the tumor involved the right kidney. All patients underwent a renal ultrasound examination followed by computed tomographic (CT) scan or magnetic resonance imaging (MRI) to confirm the diagnosis and stage the tumor clinically. All patients treated

Table II—Renal Cell Carcinoma Staging

	N.PTS	%
G1	31	39.7
G2	32	41.1
G3	15	19.2
<hr/>		
78 pts. (1980-1998)	25	29.5
(pT3aN0)	21	
(pT3N1)	2	
IV	11	14.1
<hr/>		
78 pts. (1980-1998)		

early on in the series underwent urography and some also had selective renal artery arteriography. All patients also had scintigraphic scans to assess renal function, particularly in the contralateral kidney.

The surgical approach was a midline laparotomy. In all cases surgery consisted of a radical nephrectomy including the adrenal gland, perirenal fat and Gerota's fascia, with a lymphadenectomy extending to the pre-lateral-retroaortic territories for the left kidney or the pre-lateral and retrocaval territories for the right kidney, then from the infradiaphragmatic crus to the iliac bifurcation and to the interaorto-caval territory. All patients had clear-cell renal carcinomas. According to postoperative assessment of the anatomical extent (the pathologic stage) and grade of the tumor using the Tumor-Node-

Metastasis classification of the 1997 edition of the International Union against Cancer, 4 out of the 78 patients (5.1%) had stage I tumor; 40 (51.3%) stage II tumor; 23 (29.5%) stage III tumor (21 tumor were T_{vi}N₀ and 2 were T_{ib}N₁); and 11 (14.1%) stage IV tumor (Table I). Tumor grading for cell differentiation showed that 31 patients (39.7%) had well-differentiated tumor (G₁); 32 (41.1%) moderately-differentiated (G₂); and 15 (19.2%) poorly-differentiated tumor (G₃) (Table II). Of the 40 patients with T_{vi}N₀ tumor, 20 were G₁ and 19 G₂, and of the 21 patients with T_{3a}N₀ 9 tumor were G₁ and 10 G₂. All 78 patients were available for long-term postoperative follow-up (range, 24 to 236 months after surgery). The Kaplan-Meier method was used to estimate actuarial survival in relation to stage, primary-tumor extension and grade, and the curves for the various groups were compared by the log-rank test.

Results

None of the operations led to postoperative morbidity or mortality.

Overall actuarial survival at 5 years and 10 years was 100% for stage I; 91.3% and 83.1% for stage II; 45.5% and 34.1% for stage III and 29.1% and 0 for stage IV, respectively. There was no significant difference in survival between stages I and II or between stages III and IV. Patients with stage II tumor survived significantly longer than those with stage III tumor ($p = 0.0001$) (Figure 1).

Survival differed significantly in the 40 patients whose tumor remained confined within the kidney (pT_{vi}N₀) and the 21 with malignant extension to the perirenal fat (pT_{3a}N₀) (91.3% vs 36.8% at 5 years; and 83.1% vs 22.1% at 10 years; $p = 0.000006$) (Figure 2). No significant differences were found for 5- and 10-year survival rates between patients with well-differentiated and those with moderately-differentiated tumor (82.6% vs 76.5% at 5 years; 66.7% vs 73.4% at 10 years). Conversely, survival at 5 and at 10 years differed significant-

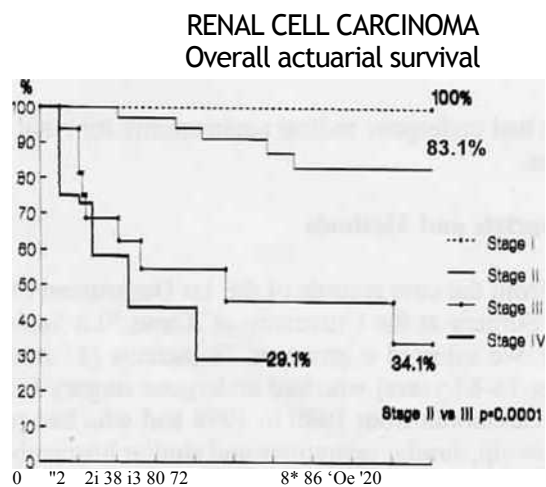
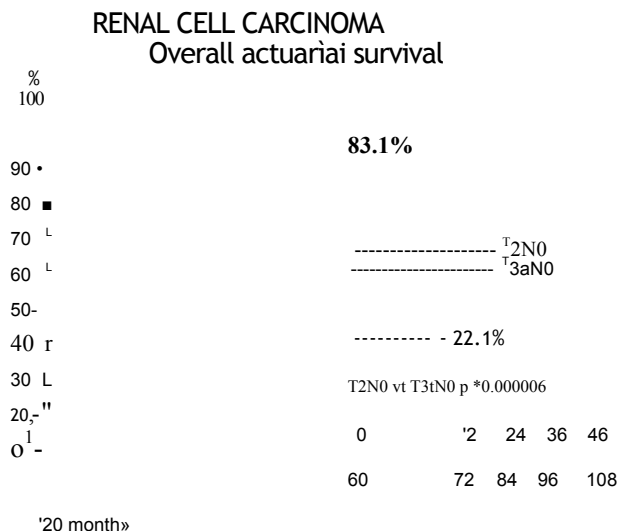


Fig. 1 - Stage related overall actuarial survival.



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Fig. 2 - Primary tumor extension related overall actuarial survival.

ly in patients with G, and in those with G, tumors ($p = 0.00005$) (none of the G, group survived at 5 years) and also between patients with G, and those with G, tumors ($p = 0.009$) (Figure 3). Stage being equal, we found no significant differences between survival in patients with G, and those with G, tumors.

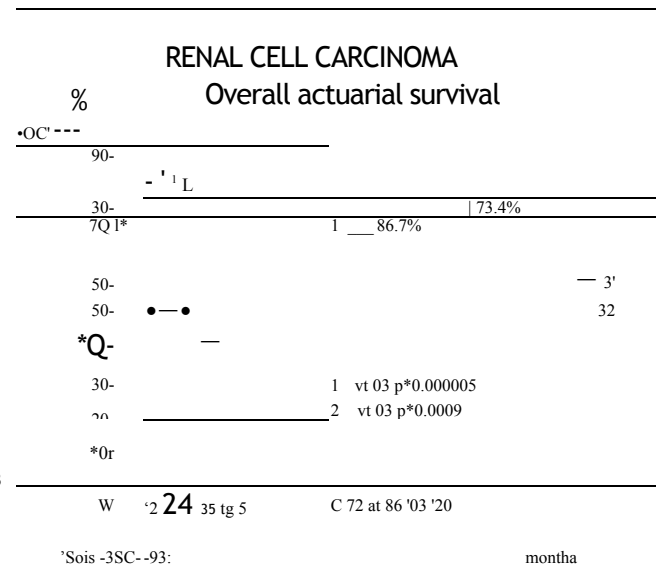
Discussion

Primary-tumor extension is an important prognostic factor in patients with renal cell carcinoma. In patients without lymph-node metastases, most investigators report better survival rates in patients with tumors confined to the kidney (T₁-T₂) than in those with tumor extension outside the organ (T₃-T₄) (1-6), though not all studies confirm this finding (7).

A review of the literature showed that according to histologic tumor grade of nuclear differentiation, tumors in higher grades (G₃) metastasize more often than those in lower grades (G₁, and G₂), with no significant differences between G₁ and G₂ (8-14).

The data we report here underline the prognostic importance of primary-tumor extension; even in patients with no lymph-node involvement, tumors involving the perirenal fat (T₃) have a significantly worse prognosis than those confined to the kidney.

Also in our patients, the grade of cellular differentiation had no influence on survival at least for well-differentiated or moderately-differentiated tumors, whereas

**Fig. 3** - Grade of nuclear differentiation related overall actuarial survival.

poorly-differentiated tumors had a significantly worse prognosis.

The absence of lymph-node metastases cannot be considered a favorable prognostic sign when the tumor has extended beyond the kidney (15-18). One reason is that renal carcinoma rarely spreads via the lymphatic route (only 6-32% of illese patients have lymph-node metastases) (19-22), in our case series 11.5%. Second, kidney lymphatic drainage varies and can involve distant lymph-node stations while regional lymph nodes remain healthy (23-25). In our series, one patient with a T₃(N₀) tumor had distant metastases in the mediastinal lymph nodes.

A wide lymphadenectomy remains a useful procedure that provides more precise information for histopathological staging without increasing morbidity or mortality. Whether adjuvant therapy improves the prognosis of patients who have T₃ tumors with grade 3 differentiation should be determined in randomized prospective studies.

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