Predictors of Survival of Advanced Renal Cell Carcinoma: Long-Term Results From Southwest Oncology Group Trial S8949

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Abbreviations and Acronyms

RCC = renal cell carcinoma

SWOG = Southwest Oncology Group

TKI = tyrosine kinase inhibitor

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Purpose: S8949 demonstrated improved overall survival for debulking nephrectomy in interferon treated patients with advanced renal cell carcinoma. We present an updated analysis of S8949, now with a median followup of 9 years. We explored clinical predictors of overall survival.

Materials and Methods: Univariate and multivariate Cox regression analysis was performed to evaluate the impact of clinical variables potentially influencing survival.

Results: Of 246 patients 241 were eligible and randomized to interferon with or without nephrectomy. Patients randomized to nephrectomy continued to have improved overall survival (HR 0.74, 95% CI 0.57–0.96, p = 0.022). Multivariate analysis showed that performance status 1 vs 0 (HR 1.95, p <0.0001), high alkaline phosphatase (HR 1.5, p = 0.002) and lung metastasis only (HR 0.73, p = 0.028) were overall survival predictors. There was no evidence of an interaction of performance status, measurable disease or lung metastases with nephrectomy (each p >0.30). In a patient subset that survived at least 90 days after randomization early progressive disease within 90 days was prognostic of overall survival in a multivariate model (HR 2.1, p <0.0001), as was performance status (HR 1.7, p = 0.0006).

Conclusions: Nephrectomy prolonged long-term overall survival in this updated analysis, supporting its role as standard therapy in patients with advanced renal cell carcinoma. A nephrectomy benefit was seen across all prespecified patient subsets. Early progressive disease and performance status were strong predictors of overall survival. These results support efforts to identify biomarkers of renal cell carcinoma resistance to treatment and early progressive disease to facilitate rational patient selection for systemic therapy.

Key Words: kidney; carcinoma, renal cell; inteferons; nephrectomy; mortality

Renal cell carcinoma is a highly heterogeneous malignancy with marked variability in disease behavior, histology and molecular biology.[1] Localized RCC generally carries a good prognosis, while extensive disease is essentially incurable. Although stage is perhaps the most important prognostic factor, many other factors, such as tumor grade, performance status and the proliferation index, have been reported to influence prognosis.

Some groups have evaluated clinical prognostic and predictive factors to aid in treatment selection and clinical trial design.[2–5] Independent prognostic factors found on multivariate analysis in various studies include an

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Table 1. *Clinical and laboratory variables in S8949*

Variable		
No. pts	241	
No. randomized to nephrectomy (%)	120	(49.8)
No. men (%)	167	(69.3)
No. progression within 90 days (%)	63	(32.5)
Median age (range)	59	(28–86)
Median gm/dl hemoglobin (range)	12.4	(6.8–18)
Median IU/l alkaline phosphatase (range)	108	(30–113)
Median mg/dl creatinine (range)	1.0	(0.4–9.0)
Median mg/dl calcium (range)	5.6	(4.4–15.4)
Median mIU/l thyroid stimulating hormone (range)	1.9	(0.01–21)

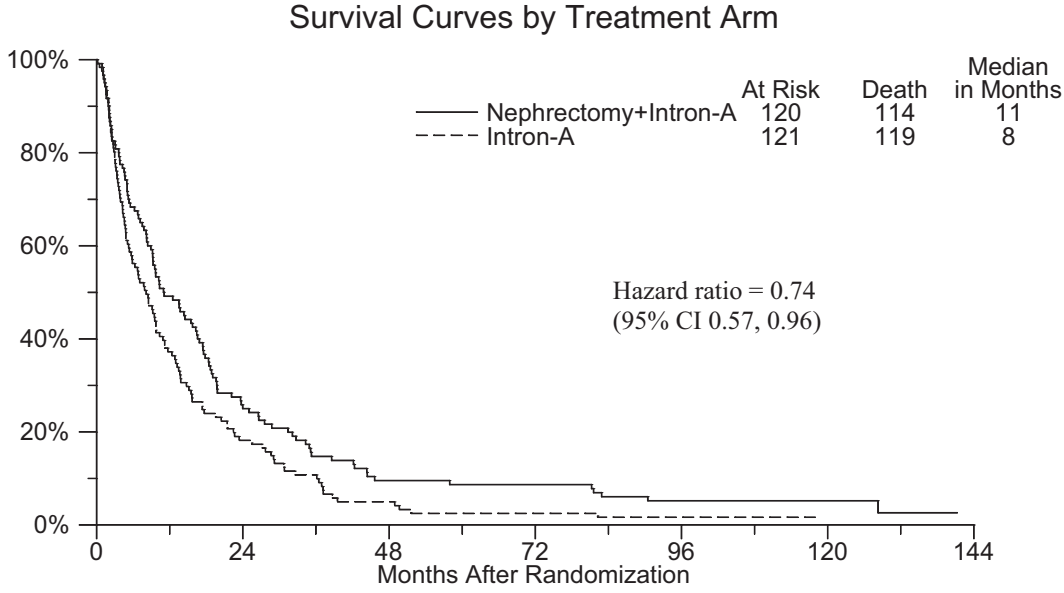
increased erythrocyte sedimentation rate, thrombocytosis, high lactate dehydrogenase, low serum hemoglobin, high serum calcium and a time from initial diagnosis to immunotherapy of less than 1 year.[6–8] In addition, some molecular tumor markers have been suggested to provide additional prognostic information.[9,10] Models including these markers promise to provide more accurate prognostic data to physicians, allowing more appropriate treatment planning and patient counseling.

S8949 was the first randomized, phase III trial to show a benefit for palliative debulking nephrectomy in patients with advanced RCC.[11] This trial provides yet another rich and mature database in which to evaluate prognostic or predictive clinical biomarkers for RCC. S8949 enrolled 241 patients with histologically confirmed RCC and a performance status of 0 or 1 without prior systemic therapy, randomizing them to interferon therapy alone or debulking nephrectomy followed by interferon. Prespecified stratification factors included performance status (1 vs 0), lung metastasis only (yes vs no) and the presence or absence of at least 1 measurable metastatic lesion that was not to be resected. As originally reported in 2001, patients randomized to the nephrectomy arm had a significant survival benefit with a median survival of 11 months vs 8 in the control arm ($p = 0.05$).[11]

We hypothesized that clinical variables collected as part of S8949 would provide prognostic and predictive information on patients with advanced RCC. We evaluated patient subsets with regard to these variables to determine whether any particular subset benefited more or less from nephrectomy, that is predictive factors, and assessed these variables for potential prognostic significance with regard to survival.

PATIENTS AND METHODS

S8949 data were updated in the current analysis, now with a median followup of 9 years. Since the original publication,[11] there have been 18 additional deaths, including 5 on the interferon arm and 13 on the nephrectomy plus interferon arm. Clinical variables were included on univariate and multivariate analysis to evaluate associations with overall survival with $p < 0.05$ considered statistically significant. In addition, these variables were evaluated in 2 Cox proportional hazard models. In model 1 all variables except progression within 90 days were assessed. Survival in this model was defined as starting from study registration to the date of death from any cause. Patients who are still alive were censored at the last contact date. In model 2 all variables were evaluated, including progression within 90 days. Landmark analysis of survival in this model was defined starting 90 days after



S8949 Kaplan-Meier overall survival curves