The comparative survival of renal leiomyosarcoma

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Introduction: *Leiomyosarcoma of the kidney and renal pelvis is a rare tumor that, on the basis of limited data, has been ascribed a particularly poor prognosis compared to other subtypes of renal malignancy. Here the population-based Surveillance, Epidemiology, and End Results (SEER) registry is used to study the survival of renal leiomyosarcomas.*

Methods: *There were 95,935 cases of invasive cancer of the kidney and renal pelvis retrieved from the SEER registry to provide 112 cases of leiomyosarcoma. Kaplan-Meier survival estimates and Cox proportional hazard models were constructed to compare the survival of leiomyosarcomas to other renal malignancies.*

Results: *Leiomyosarcomas constituted 0.12% of all invasive renal malignancies. They exhibited a median overall survival of 25 months, with a 25% 5-year overall survival, and a 60% 5-year cause-specific survival. Multivariate analysis of all renal malignancies together revealed that cancer stage was the strongest predictor for overall survival followed by age, histological grade, histological subtype, tumor size, and gender. The hazard ratio for leiomyosarcoma in this analysis was intermediate compared to the other malignancies. When leiomyosarcomas were analyzed separately, the major determinants to overall survival were stage and age at diagnosis. Kaplan-Meier analysis revealed that the overall survival curve for renal leiomyosarcoma essentially superimposed that of transitional cell carcinoma, and was better than that of clear cell carcinoma. These results provide a more optimistic outlook than has been conventionally afforded to this tumor.*

Key Words: leiomyosarcoma, renal malignancies, subtype analysis, prognostic factors

Introduction

Leiomyosarcoma of the kidney is a rare tumor that comprises less than one percent of all renal malignancies.[1] Published reports would indicate that renal leiomyosarcoma tends to present with higher grade lesions, with distant spread, and with a female predominance.[2,3] There have been over 80 single case reports of unilateral leiomyosarcomas of the kidney or renal pelvis,[3-86] five reported cases of bilateral tumors,[87-90] as well as multiple published series ranging in size from two to 21cases,[1,2,87,89,91-103] which in total afford over 190 cases of renal leiomyosarcoma. Reviews of such assorted data have provided overall survival estimates of less than 2 years,[38,60,82,104] reflecting a poorer prognosis than for other malignant renal neoplasms.[40]

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However, the lack of uniformly applied clinicopathological assessments in these assorted reports, as well as the potential for selection bias inherent to small case series, could prejudice such assessments. Indeed, in the absence of a sizable collection of uniformly evaluated data, more detailed predictive assessments might best be inferred from the behavior of other visceral sarcomas. For instance, retroperitoneal sarcomas with high tumor grade, incomplete resection, nodal metastasis, or distant metastasis have a poor prognosis,[105-109] and presumably renal leiomyosarcomas would behave similarly.

The Surveillance, Epidemiology, and End Results (SEER) program of the United States National Cancer Institute provides an extensive population-based registry for various cancers that has been collected with a high degree of uniformity. This database could potentially permit a detailed survival analysis of renal leiomyosarcoma, with comparisons based upon other histological subtypes of renal malignancies.[110] An observational study of renal malignancies will be presented here, based upon these SEER data. The overall and cause-specific survival of renal leiomyosarcomas will be estimated along with proportional hazard analyses of risk factors for survival.

Methods

Study cohorts and data

Population-based data were obtained from the SEER Public-Use registry, released April 2006, using the November 2005 submission (1973-2003). The study was restricted to histologically confirmed invasive renal malignancies. Two historical cohorts were studied: those diagnosed with any invasive malignancy of the kidney or renal pelvis, and those diagnosed with leiomyosarcomas of the kidney or renal pelvis. The first cohort served as a control group (assuming the contribution of renal leiomyosarcomas to this larger cohort would be negligible) to which the behavior of renal leiomyosarcomas could then be compared.

Data were retrieved with respect to the follow-up time, the age at diagnosis of the renal cancer, gender, race and ethnicity, the SEER historical stage of the cancer, tumor size, the histological grade and the histological subtypes of the renal cancer, as well as treatment. The SEER data had no personal identifiers and so were in compliance with Canadian privacy legislation; it was thus not subject to review by the Ottawa Hospital Research Ethics Board.

Statistical methods

Descriptive statistics included the total number of cases, the gender ratio, median follow-up time, and the numbers of cases within each category of grade, and SEER historical stage. Median survival times were obtained by the method of Kaplan and Meier. Both overall and cause-specific survivals were assessed. Kaplan-Meier survival estimates were compared using Gehan's generalized Wilcoxon test.

Cox proportional hazard analyses were performed with respect to overall survival, and using histological subtype, age at diagnosis, gender, histological grade, stage, and tumor size as covariates. Age and tumor size were treated as continuous variates; the other variates were treated categorically. Hazard ratios, and their respective 95% confidence intervals (CIs), were estimated from these analyses. These 95% CIs were used to determine whether or not statistically significant differences were evident between different histological subtypes of the renal tumors with respect to renal leiomyosarcomas. Probability (p) values were obtained from the Wald chi square test; the Wald statistic (WS), itself, was used to assess the strength of association of the individual covariates with overall survival.

Results

The study retrieved a total of 95,935 cases with invasive cancers of the kidney and renal pelvis, of which 112 (0.12%) were leiomyosarcomas. Characteristic features of the two cohorts are summarized in Table 1. Fifty-nine percent of the leiomyosarcoma cases were in females, in contrast to only 38% of the control cohort. Fifty-two percent of the leiomyosarcomas were localized to the left kidney; one case (1%) occurred bilaterally. Other features included a greater proportion of anaplastic cancers amongst the leiomyosarcomas, as well a propensity towards regional and distant spread of disease at the time of diagnosis, Table 1.

For these 95,935 cases the primary management was surgical: 19% of cases had no cancer-directed surgery; another 19% had an unspecified form of surgery; 6% had localized surgery (i.e., local excision or subtotal nephrectomy); 48% were treated with total or radical nephrectomy, and for 8% of cases the surgical treatment was unknown. In addition, 17% of cases received external beam radiotherapy. These treatment-related parameters were found to be not informative on the initial exploration of Cox models, and thus were not included in the proportional hazards analyses reported here.

TABLE 1. **Characteristics of the study populations**

	All malignancies of kidney and renal pelvis	**Leiomyosarcomas of kidney and renal pelvis**
Total # cases	95,935	112
Gender ratio: # cases ♀/♂(%♀)	36,282/59,653 (37.8)	66/112 (58.9)
Age at diagnosis: mean (SD)	63.3 (15.8) yr	58.1 (13.4) yr
Grade: # cases (%)		
Well differentiated, grade 1	7,949 (8.3)	3 (2.7)
Moderately differentiated, grade 2	19,174 (20.0)	12 (10.7)
Poorly differentiated, grade 3	12,015 (12.5)	16 (14.3)
Anaplastic, grade 4	3,642 (3.8)	17 (15.2)
Unknown	53,155 (55.4)	64 (57.1)
SEER historic stage: # cases (%)		
Localized	48,840 (50.9)	34 (30.4)
Regional	20,142 (21.0)	32 (28.6)
Distant	20,286 (21.1)	40 (35.7)
Unknown	6,667 (7.0)	6 (5.3)
Median follow-up time	23 months	21 months

SD - standard deviation

Kaplan-Meier analysis revealed that 25% of the leiomyosarcoma cases survived over 5 years from diagnosis, and that the 5-year cause-specific survival was 60%, Figure 1. Cox proportional hazard analysis of all renal malignancies together revealed significant associations between overall survival and specific tumor histology, age at diagnosis, larger tumor size, gender, tumor stage, and tumor grade, Table 2. Stage was the strongest predictor for overall survival (WS = 14,306, $p < 0.001$), followed by age (WS = 3,645, $p < 0.001$), histological grade (WS = 887, $p < 0.001$), histological subtype (WS = 618, $p < 0.001$), tumor size (WS = 487, $p < 0.001$), and gender (WS = 61, $p < 0.001$).

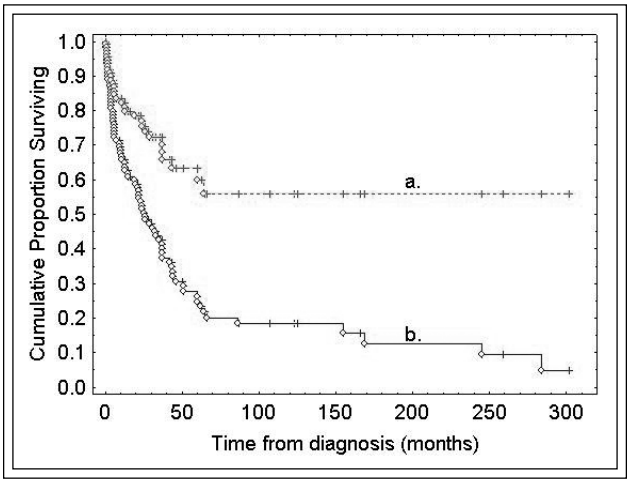

Figure 1. Survival with renal leiomyosarcoma. Kaplan-Meier methods were used to calculate cause-specific (a) and overall (b) survivals. The cumulative proportion of patients surviving was plotted versus the elapsed time from diagnosis. Median overall survival was 25 months.

With respect to the influence of histological subtype on overall survival, leiomyosarcomas revealed an intermediate hazard ratio with significantly lower hazard ratios for clear cell adenocarcinoma, papillary adenocarcinoma, nephroblastoma, granular cell carcinoma, bronchoalveolar carcinoma, and liposarcoma, Table 2. On the other, hand, malignant rhabdoid tumors and squamous cell carcinomas had worse hazard ratios, Table 2. Kaplan Meier analyses similarly revealed an intermediate survival behavior for renal leiomyosarcoma, Figure 2. In these latter analyses the survival curve for leiomyosarcoma was superimposed on that from transitional cell carcinoma, and was better than for clear cell carcinomas. These survival differences were all statistically significant ($p \leq 0.0001$) with the exception of the comparison of leiomyosarcoma to transitional cell carcinoma ($p > 0.05$). The apparent contradiction in comparative overall survival of leiomyosarcoma and clear cell carcinoma obtained from the proportional hazards analysis and the Kaplan-Meier analyses can be attributed to the fact that the

TABLE 2. **Multivariate analysis for all malignancies of the kidney and renal pelvis (n = 95,935)***

Covariates	Frequency (%)	Hazard ratio (95% CI)
SEER histology		
Clear cell adenocarcinoma	73.93	1.00 (index category)†
Papillary transitional cell carcinoma	5.15	1.01 (0.94 - 1.07)
Transitional cell carcinoma	5.05	1.38 (1.30 - 1.47)
Adenocarcinoma	3.25	1.22 (1.12 - 1.32)
Carcinoma, NOS	3.05	1.85 (1.67 - 1.97)
Papillary adenocarcinoma	2.38	0.77 (0.67 - 0.86)†
Nephroblastoma	1.92	0.54 (0.44 - 0.67)†
Granular cell carcinoma	1.67	0.95 (0.87 - 1.04)†
Malignant neoplasm of kidney/renal pelvis	1.63	1.49 (1.34 - 1.66)
Bronchoalveolar carcinoma	0.58	0.79 (0.64 - 0.97)†
Papillary carcinoma	0.35	1.11 (0.88 - 1.39)
Squamous cell carcinoma	0.32	2.58 (2.14 - 3.11)‡
Sarcoma, NOS	0.16	1.46 (1.11 - 1.92)
Leiomyosarcoma	**0.12**	**1.42 (1.04 - 1.94)**
Clear cell sarcoma	0.09	2.15 (1.47 - 3.13)
Small cell carcinoma	0.06	1.87 (1.30 - 2.70)
Liposarcoma	0.06	0.50 (0.25 -0.99)†
Giant and spindle cell carcinoma	0.05	2.41 (1.63 - 3.57)
Solid carcinoma	0.04	1.09 (0.54 - 2.17)
Mucinous adenocarcinoma	0.04	1.75 (0.83 - 3.67)
Neuroblastoma	0.04	3.27 (1.47 - 7.31)
Malignant rhabdoid tumor	0.04	5.42 (3.07 - 9.56)‡
Carcinosarcoma	0.03	2.59 (1.61 - 4.17)
Age at diagnosis (yr)		1.03 (1.03 - 1.04)
Tumor size (mm)		1.002 (1.002 - 1.003)
Female gender	38	0.90 (0.88 - 0.92)
Histological grade		
Well differentiated, grade 1	8.3	0.96 (0.91 - 1.02)
Moderately differentiated, grade 2	20	1.00 (index category)
Poorly differentiated, grade 3	13	1.47 (1.40 - 1.54)
Anaplastic, grade 4	3.8	1.94 (1.83 - 2.07)
Unknown	55	1.52 (1.48 - 1.59)
SEER historic stage		
Localized disease	51	1.00 (index category)
Regional disease	21	1.79 (1.73 - 1.85)
Distant disease	21	7.50 (7.26 - 7.76)
Unknown	7.0	3.00 (2.77 - 3.17)

*Based on a Cox proportional hazards analysis of overall survival. There were no missing values in this analysis.
†Hazard ratios significantly lower than for leiomyosarcoma
‡Hazard ratios significantly higher than for leiomyosarcoma
CI - confidence interval; NOS - not otherwise specified

proportional hazard analyses also compensated for any disparities between the two groups with respect to age at diagnosis, gender, tumor size, grade and stage.

A separate proportional hazard analysis was performed with the leiomyosarcoma cases alone. For these 112 cases the distribution of different surgical procedures was similar to that seen with the larger

TABLE 3. **Multivariate analysis for leiomyosarcomas of the kidney and renal pelvis (n = 112)**

Covariates	Frequency (%)	Hazard ratio (95% CI)	
		Based on overall survival	Based on cause-specific survival
Age at diagnosis		1.028 (1.001 - 1.028)*	1.031 (1.001 - 1.063)*
Female gender	59	0.80 (0.50 - 1.30)	0.84 (0.38 - 1.84)
Histological grade			
Well differentiated, grade 1	2.7	1.34 (0.65 - 4.96)	1.89 (0.19 - 19.38)
Moderately differentiated, grade 2	11	1.00 (index category)	1.00 (index category)
Poorly differentiated, grade 3	14	1.79 (0.65 - 4.96)	1.10 (0.22 - 5.60)
Anaplastic, grade 4	15	1.32 (0.48 - 3.60)	0.56 (0.09 - 3.58)
Unknown	57	1.52 (0.68 - 3.38)	1.51 (0.44 - 5.12)
SEER historic stage			
Localized	30	1.00 (index category)	1.00 (index category)
Regional	29	0.95 (0.51 - 1.78)	1.43 (0.44 - 4.66)
Distant	36	4.48 (2.40 - 8.37)*	7.92 (2.50 -25 .05)*
Unknown	5.4	6.05 (2.05 - 17.83)	13.10 (2.60 - 66.11)

*Statistical significance: $p < 0.05$
There were no missing values in this analysis.
CI - confidence interval

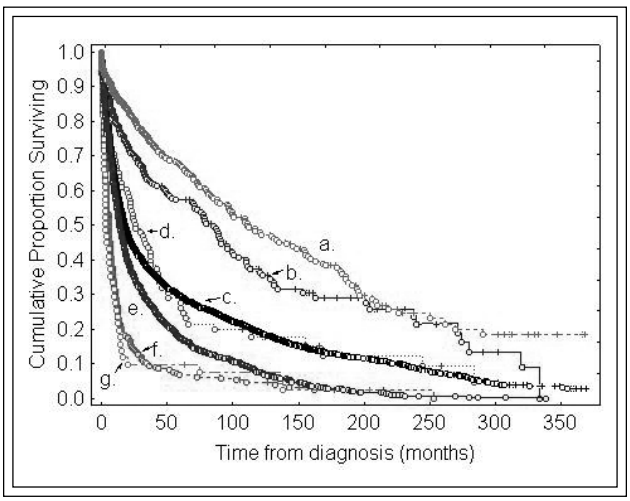

Figure 2. Comparative overall survival for selected renal malignancies. Kaplan-Meier survival plots are provided here for the following histological subtypes: a) papillary adenocarcinoma, b) papillary carcinoma, c) transitional cell carcinoma, d) leiomyosarcoma, e) clear cell adenocarcinoma, f) squamous cell carcinoma, g) small cell carcinoma. The overall survival for leiomyosarcoma was comparable to that of transitional cell carcinoma and was intermediate within the group of different renal tumors.

group of renal cancers. A multivariate analysis showed that an advanced stage at diagnosis and age were associated with increased hazard ratios for both overall and cause-specific survival, however gender and histological grade had no measurable influence, Table 3. This lack of association of gender and grade with survival likely reflected a lack of statistical power in the analysis. In addition, multivariate analysis with the number of involved nodes, the use of radiotherapy, and the type of surgical management as covariates, revealed no significant associations and thus were not included in the analysis provided here. As with general renal malignancies, stage was the predominant determinant for overall survival (WS = 33, $p < 0.001$), followed by age at diagnosis (WS = 9, $p = 0.003$).

Discussion

SEER provides probably the largest single collection of data available regarding renal leiomyosarcoma; however, this database does have some limitations. Tumor grade was not specified in 57% of cases; neither was there information regarding the number of mitoses, the presence of tumor necrosis, the completeness of surgical resection, nor details regarding recurrences. As well, the tumor histology provided by SEER had not been not subject to central review. Some insight into the effect of the lack of

histological review can be gleaned from SEER lung tumor cases, where a central pathology review of was obtained: Although there were minor discrepancies, the SEER histological diagnoses were found to be quite reliable.[111] Although there are limitations with the SEER database, overall it has been regarded as a valuable tool for the assessment of tumor behavior.[111]

The results obtained here should be compared to an analysis reported by Patard et al, from an international database of 4063 cases of renal cell carcinoma.[110] Their multivariate analysis showed that stage, grade and performance status were significant predictors for survival whereas the histological subtypes of renal cell carcinoma were not. One major difference between their analysis and that reported here was the size of the database. SEER provided 95,935 cases for analysis, allowing for greater statistical power and the inclusion of a larger range of renal malignancy.

Historically, renal leiomyosarcoma has been regarded to have a poor prognosis relative to other renal malignancies,[40] yet the SEER data revealed that the 25-month median and 25% 5-year overall survivals for these tumors were comparable to other renal tumors. Leiomyosarcoma of the kidney should more properly be considered to exhibit an intermediate survival relative to the range of behavior for other renal malignancies.

Observational data such as these do not allow conclusions to be drawn regarding the effect of different management modalities. The opinion of a number of experts would consider radical nephrectomy to be the treatment of choice.[60,77,83,102] Beyond this, given the rarity of renal leiomyosarcomas and the lack of prospective studies, it is difficult to draw conclusions from the literature regarding the efficacy of adjuvant radiotherapy or chemotherapy.

In summary, leiomyosarcoma of the kidney and renal pelvis are relatively rare tumors, constituting 0.12% of invasive renal malignancies. The SEER analysis presented here revealed a median overall survival of 25 months with a 5-year overall survival of 25%. Such survival results are comparable to other renal malignancies, and thus prognostications regarding this tumor should be made in this relative context. □

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