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Original article

The effect of gender and age on kidney cancer survival: Younger age is an independent prognostic factor in women with renal cell carcinoma

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Abstract

Objective: Gender-specific differences in incidence of renal cell carcinoma (RCC) and its outcome have previously been reported. We used age as a surrogate to test whether this might be hormone-related in a large international RCC cohort.

Methods and Materials: This study included patients treated by nephrectomy at 10 international academic centers. Clinicopathologic features were assessed using chi-square and the Student *t*-tests. Kaplan-Meier survival estimates and Cox proportional hazards models addressed the effect of gender and age on disease-specific survival.

Results: Of the 5,654 patients, 3,777 (67%) were men and 1,877 (33%) were women. Generally, women presented at lower T stages ($P < 0.001$), had fewer metastases ($P < 0.001$), and had lower-grade tumors ($P < 0.001$). Women more frequently had clear-cell (87% vs. 82%) and less frequently had papillary RCC (7% vs. 12%) than men ($P < 0.001$). Women had a 19% reduced risk of death from RCC than men (hazard ratio 0.81, 95% confidence interval 0.73–0.90, $P < 0.001$). The survival advantage for women was present to the greatest degree in the age group <42 years ($P = 0.0136$) and in women aged 42 to 58 years ($P < 0.001$), but was not apparent in patients aged 59 years and older ($P = 0.248$). Age was an independent predictor of disease-specific survival in women (hazard ratio 1.011, 95% confidence interval 1.004–1.019, $P = 0.004$), but not in men.

Conclusions: As a group, women present with less advanced tumors, leading to a 19% reduced risk of RCC-specific death compared with men. This survival difference is present only in patients aged <59 years. Because this gender-based survival difference is not related to pathologic features, the role of hormonal effects on the development and progression of RCC needs to be investigated.

Keywords: Gender; Age groups; Sex hormones; Epidemiology; Renal cell carcinoma

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1. Introduction

Gender-based survival differences have been observed in many regional and international tumor registries across many different tumor types [1–3]. In many of these studies, women demonstrate a survival advantage compared with men across numerous tumor types. Whether these survival differences reflect biologic or cultural or both factors remains controversial. If biologic, one potential mechanism to consider would be the possible protective effect of sex hormones on oncogenic processes [4,5]. Renal cell carcinoma (RCC) occurs twice as often in men as in women; however, the influence of gender on stage, grade, histologic subtype, and survival has not been studied in detail. If this imbalance in the incidence of RCC is related to gender-specific hormone levels, age could be a further explanatory variable. To test this hypothesis, we sought to examine the possible contribution of sex hormones to cancer-specific survival in RCC, using age as a surrogate for hormone status, in a large international RCC cohort.

2. Material and Methods

This multi-institutional cohort study included records on 5,654 patients diagnosed with unilateral RCC and treated by nephrectomy between 1974 and 2006 at the following centers: Rennes, Creteil, Saint-Etienne, Necker Paris, Toulouse, Bordeaux, Rouen, Lyon (France), Magdeburg (Germany), Benevento (Italy), and the University of California at Los Angeles (USA). Institutional review board approvals were attained at each respective institution. Approximately 40% of the patients were from the USA. Clinicopathologic data included age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), pathologic stage, Fuhrman grade, and histologic subtype. Pathologic stage was assessed by the 2002 American Joint Committee on Cancer tumor, nodes, metastases (TNM) classification, and the histologic subtype was assigned according to the Heidelberg classification of renal tumors [6]. Median follow-up was 36 months. Records were available for review with 10 years of follow-up on 523 patients. The selection of the age cut-points as surrogate measures of sex hormone status was based on multiple epidemiologic studies regarding menopause in North America. In these studies, greater than 95% of women are found to be hormone-intact at age 42, whereas 97% of women have undergone primary ovarian failure at the age 58 [7]. We used these data to yield 3 epidemiologically based age groups as surrogate measures of hormonal status.

Differences in gender, age, T, N, and M stages, Fuhrman grade, and histologic subtype were evaluated with chi-square and the Student *t*-tests for categorical and continuous data, respectively. Cancer-specific survival was calculated from the date of nephrectomy to the date of death from RCC or last contact. Survival probabilities were estimated with the Kaplan-Meier method, and the log-rank test was applied to compare survival curves. Univariate and multivariate Cox proportional hazards analyses were used to assess the relative effect of gender and age on cancer-specific survival. All statistical tests were 2-sided and performed at a significance level of 0.05. Analysis was performed with the use of STATA 10.1 software package (College Station, TX).

Table 1
General clinicopathologic and demographic data

	Male (%), $n = 3,777$	Female (%), $n = 1,877$	Total (%), $n = 5,654$
Age at diagnosis			
Median	61	62	61
ECOG PS*			
0	2,404 (64)	1,121 (60)	3,535 (62)
1	1,318 (35)	727 (39)	2,045 (36)
≥2	55 (2)	29 (2)	84 (2)
T stage*			
T1	1,664 (44)	889 (47)	2,553 (45)
T2	499 (13)	286 (15)	785 (14)
T3	1,487 (39)	652 (35)	2,139 (38)
T4	127 (3)	50 (3)	177 (3)
N stage			
N0	3,359 (89)	1,665 (89)	5,024 (89)
N1	273 (7)	127 (7)	400 (7)
N2	145 (4)	85 (5)	230 (4)
M stage*			
M0	2,832 (75)	1,515 (81)	4,337 (77)
M1	945 (25)	362 (19)	1,307 (23)
Fuhrman grade*			
G1	721 (19)	414 (22)	1,135 (20)
G2	1,499 (40)	799 (43)	2,298 (41)
G3	1,236 (33)	512 (27)	1,748 (31)
G4	321 (8)	152 (8)	473 (8)
Histology*			
Clear cell	3,108 (82)	1,631 (87)	4,739 (84)
Papillary	468 (12)	135 (7)	603 (11)
Chromophobe	137 (4)	79 (4)	216 (4)
Collecting duct	12 (<1)	6 (<1)	18 (<1)
Unclassified	52 (1)	26 (1)	78 (1)

*$P < 0.05$.

3. Results

3.1. Clinicopathologic factors

Of the 5,654 patients who comprised the study population, 3,777 (67%) were men and 1,877 (33%) were women. Median age, ethnicity, rates of obesity, hypertension, and tobacco use were not significantly different between genders. Clinicopathologic differences are given in Table 1. Significantly more men than women had an ECOG PS of 0, 64% vs. 60% ($P < 0.05$). Women were more likely to have an ECOG PS of 1, 39% vs. 35% ($P < 0.05$). Women also presented with lower-stage ($P < 0.001$), lower-grade ($P < 0.001$), and less frequent synchronous metastatic disease ($P < 0.001$) compared with men. Women were more likely to have clear-cell histology (87% vs. 82%) and less likely to have papillary RCC (7% vs. 12%) than men (<0.001).