AGE AND GENDER RELATED DIFFERENCES IN RENAL CELL CARCINOMA IN A EUROPEAN COHORT

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ABSTRACT

Purpose
To evaluate the influence of age on gender related differences in renal cell carcinoma (RCC) presentation of patients operated between 1995 and 2005 in a European country and to assess the trend in missing pathological data.

Material and Methods
Data of all patients who underwent radical or partial nephrectomy for RCC during 1995-2005 in the Netherlands were retrospectively collected from the prospective PALGA database. Patients were divided into five cohorts based on age at surgery (≤40; 41-50; 51-60; 61-70; and >70 years). Variables evaluated were gender differences for age, tumour size, subtype, tumour stage and Fuhrman grade.

Results
A higher mean age in women was only observed in patients older than 70 years (p<0.001). Male to female ratio was 2:1 between 41-60 years and 1.2:1 in patients older than 70. Compared to men, women had smaller tumour size between 51-60 years (p=0.03), tumour stage pT3 was less frequent from 41 years onward (p=0.02) and grade 2 was less frequent from 61 years onward (p<0.001). Percentages of tumours with missing stage (14.9%), subtype (52.2%) and grade (47.1%) diminished substantially during the study period (p<0.001).

Conclusions
An older age in women presenting at surgery for RCC was only prevalent in patients over 70 years. The male to female ratio was almost equal in patients over 70 years, compared to 2:1 between 41 and 60 years. Women presented with less pT3 tumours than men from the age of 41 years onwards. Missing pathological data diminished significantly between 1995 and 2005.

INTRODUCTION

Broad epidemiological studies from United States databases (NCDB (National Cancer Database) and SEER (Surveillance Epidemiology and End Results)) have independently explored gender differences in the presentation of renal cell carcinoma. Their conclusions indicated that women were more likely to present with RCC at an older age, with lower stage and smaller tumours when compared to men 1,2. These gender discrepancies remain poorly understood. Suggested hypotheses, including hormonal influence, occupational exposure to chemicals, differences in symptomatic presentation and imaging patterns, do not provide sufficient explanation 3-5.

Currently large population-based assessment of RCC differences between genders is only available for the USA and data extrapolation to the European population has simply been assumed. European or Asian studies are limited by their retrospective nature and by inclusion of data originating mostly in reference centres 6. Furthermore careful interpretation is warranted due to the fact that the existent databases do not provide with a complete national coverage and contain large amounts of missing pathological data, concerning subtype, stage and grade 1,2.

PALGA (Pathological Anatomical National Automated Archive) is a Dutch nationwide pathology network and archive. The database provides pathology reports generated in all pathological laboratories in the Netherlands from 1991 onwards. Central reporting to PALGA became mandatory in 1995 7.

Objectives of this study are to evaluate the influence of age on gender related differences in RCC presentation of all operated tumours between 1995 and 2005 in the Netherlands, using the PALGA database. Furthermore we assessed the amount of missing pathological data in our cohort and related trends in missing diagnoses.

MATERIAL AND METHODS

Patient selection
All excerpts from patients who underwent radical and partial nephrectomy for a primary renal tumour during the period 1995-2005 were retrospectively retrieved from the prospectively collected PALGA database. This database automatically collects abstracts from all pathology reports generated in all pathological laboratories in the
Netherlands on a daily basis. Age at surgery and gender are mandatory in each report. The following terms were used to select renal tumours: kidney, metanephric adenoma, chromophobe adenoma, eosinophilic adenoma, adenopapilloma, adenoma and all malignancies except carcinoma in situ. Tumour biopsies, primary renal pelvic tumours, ureteric tumours and metastases were excluded (as described in our previous study). To attain a cohort of RCC patients, rare kidney tumours were excluded, see Figure 1.

Figure 1. Selection algorithm for study cases

**Variables**
The following variables were analysed: gender, age at surgery, maximal tumour diameter in centimetres (as mentioned in the pathology report) and histological subtype. Tumours were staged according to the TNM 2002 classification and Fuhrman grade was converted into a 3-tiers grading system merging grade 1 with grade 2.

**Statistical analyses**
To evaluate the influence of age on gender related differences patients were divided into five cohorts based on their age at surgery (40 years or younger; 41 through 50; 51 through 60; 61 through 70; and older than 70 years). Separate analyses were done for each sub-cohort. To evaluate whether our results would be better represented using standardized age groups, we performed an additional evaluation based on the World Health Organisation (WHO) age groups (≤44; 45-64; 65-74; 75-84; ≥85 years). Continuous variables between genders were compared by the independent samples T–test. The Chi-square test was used for comparison of categorical variables. Trends were evaluated using the Chi-square Linear-by-Linear association. All tests were two-tailed and a p-value of 0.05 was considered statistically significant. Data was assed using Predictive Analytics Software Statistics 18.0.

**RESULTS**
Of the 11619 patients included 7085 (61.0%) were male and 4534 (39.0%) were female. Table 1 displays detailed patient’s characteristics of the entire cohort. Gender differences in incidence, age and tumour size are described in table 2 and differences in tumour stage in table 3. The most notable discrepancies between genders in the age sub-cohorts are described below.

**Sex distribution**
The male to female ratio was 2:1 in ages 41-60 years and nearly equally divided in the oldest patients.

**Age at surgery**
A higher mean age at surgery was only observed in women older than 70 years. In patients of 40 years and younger, the mean age was lower in women than in men.
Table 1. Characteristics of the overall population, pT3c and pT4 tumours are not reported in this table.

<table>
<thead>
<tr>
<th></th>
<th>Male (n=7085, (61.0%))</th>
<th>Female (n=4534, (39.0%))</th>
<th>p- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age±sd (years)</td>
<td>62.6 ± 11.5</td>
<td>64.7 ± 12.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean tumoursize±sd (cm)*</td>
<td>7.1 ± 3.7</td>
<td>6.8 ± 3.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1</td>
<td>2573 (36.3%)</td>
<td>1827 (40.3%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>pT1a</td>
<td>1161 (16.4%)</td>
<td>836 (18.4%)</td>
<td>0.004*</td>
</tr>
<tr>
<td>pT1b</td>
<td>1412 (19.9%)</td>
<td>991 (21.9%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>pT2</td>
<td>1036 (14.6%)</td>
<td>705 (15.8%)</td>
<td>0.17</td>
</tr>
<tr>
<td>pT3</td>
<td>2327 (32.8%)</td>
<td>1249 (27.5%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>pT3a</td>
<td>967 (13.6%)</td>
<td>485 (10.7%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>pT3b</td>
<td>1295 (18.3%)</td>
<td>727 (16.0%)</td>
<td>0.002*</td>
</tr>
<tr>
<td>missing</td>
<td>1043 (14.7%)</td>
<td>692 (15.3%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Subtype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearcell</td>
<td>2700 (38.1%)</td>
<td>1810 (39.9%)</td>
<td>0.051</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>152 (2.1%)</td>
<td>94 (2.1%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Papillary</td>
<td>616 (8.7%)</td>
<td>188 (4.1%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>RCCNOS</td>
<td>3617 (51.1%)</td>
<td>2442 (53.9%)</td>
<td>0.003*</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1895 (26.7%)</td>
<td>1259 (28.7%)</td>
<td>0.23</td>
</tr>
<tr>
<td>2</td>
<td>1328 (18.7%)</td>
<td>720 (15.9%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>3</td>
<td>598 (8.4%)</td>
<td>345 (7.6%)</td>
<td>0.11</td>
</tr>
<tr>
<td>missing</td>
<td>3264 (46.1%)</td>
<td>2210 (48.7%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2. Sex ratio, mean age and mean tumour size in men and women in the different age cohorts.

<table>
<thead>
<tr>
<th>Age cohorts</th>
<th>&lt;40 yrs</th>
<th>41-50 yrs</th>
<th>51-60 yrs</th>
<th>61-70 yrs</th>
<th>&gt;70 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>p- value</td>
<td>n (%)</td>
<td>p- value</td>
<td>n (%)</td>
<td>p- value</td>
</tr>
<tr>
<td>Stage</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>pT1</td>
<td>11 (45.9%)</td>
<td>310 (35.9%)</td>
<td>0.33</td>
<td>814 (34.5%)</td>
<td>3841 (37.4%)</td>
</tr>
<tr>
<td>pT2</td>
<td>46 (19.0%)</td>
<td>165 (19.3%)</td>
<td>0.07</td>
<td>378 (40.6%)</td>
<td>571 (40.2%)</td>
</tr>
<tr>
<td>pT3</td>
<td>34 (21.1%)</td>
<td>167 (16.8%)</td>
<td>0.23</td>
<td>300 (18.3%)</td>
<td>277 (12.3%)</td>
</tr>
</tbody>
</table>

Table 3. Tumour stage (TNM 2002) in men and women by age cohort.

* p=<0.05

Pathology

A significantly women smaller tumour size was only seen in patients between 51 and 60 years (p=0.03). There was a significant increase in the number of small renal masses (size ≤4cm) from 1995-2005 (21.7% to 27.2%; p<0.001), mainly because an increase in males (21.0% to 28.0%, p=0.001; females 22.8%-26.0%, p=0.22).

From the age of 51 onwards the incidence of the papillary subtype was at least twice higher in men than in women (p<0.001).

Grade 2 was less frequent in women aged 61-70 (p=0.02) and older than 70 years compared to men (p<0.001).

Stage

Tumour stage pT3 was less frequent in women, except in patients younger than 40 years. Compared to their male counterparts, pT1 tumours were more frequent in women aged 51-60 (p=0.002) and older than 70 years (p=0.01).

WHO based-age categories

Using the WHO based age groups patient distribution was as followed; ≤44 years, n=764; 45-64 years, n=4903; 65-74 years, n=3885; 75-84 years n=1920; ≥85 years, n=147. Women were younger than men in the group ≤44 years (p=0.001) and older in the group 45-64 (56.5 vs. 55.9 years, p<0.001) and 75-84 years (78.2 vs. 77.9 years, p=0.01). Women had significantly smaller tumour size between 45 and 64 years, p=0.001) and ≥85 (p=0.004). More T1 tumours (resp. p=0.001, p=0.01) and less T3 tumours (resp. p=0.001, p=0.008) were seen in women compared to men in patients 45-64 and 65-74 years.
Missing data
Age and gender had no missing values. Tumour size was missing in 21.5%, but stage was determined in 85.1% of the cases. The percentage of tumours with a missing stage (14.9%) and grade (47.1%) diminished during the decade for both genders (p<0.001). Between 1995 and 2005 the frequencies of the Clear Cell, Papillary and Chromophobe subtype increased and tumours regarded as RCC not otherwise specified (NOS) (overall 52.2%) decreased in both men and women (p<0.001, except Papillary subtype in women (p=0.002)). These observations are shown in Figures 2 and 3.

DISCUSSION
This study explored the age distribution of gender discrepancies of RCC at the time of surgery. Our data contained all operated renal tumours during one decade in the Netherlands. Gender related age differences were only observed either in patients older than 70 years or younger than 40. Overall the male to female ratio was 2:1 in patients between 41 and 60 and decreased to 1.2:1 in patients older than 70 years. Women presented with less pT3 tumours from 40 years onwards, although statistical differences in tumour size were only found in the range 51-60 years. From 50 years onwards Papillary subtype was twice more prevalent in men than in women. Missing data on subtype and grade was considerable, but decreased significantly over time.

In concordance with large population based US studies assessing gender differences in RCC, overall women had a higher age at surgery.
compared to men. However in our data higher age in women was only observed in patients older than 70 years. Between ages 41-70 mean age at surgery was the same for both genders and in the subgroup younger than 40 years women were younger. The pronounced age-gender differences observed in the latter group could not compensate for the larger group of patients older than 70 years.

Age-gender related differences of RCC at surgery have been scarcely explored and in general literature regarding RCC in elderly patients is limited.

An important confounder of our observations can be the overall survival in the general population. In the Netherlands the male:female ratio for persons older than 70 years between 1995 and 2005 was approximately 1:1.6. This could have led to a higher crude number of women operated for RCC at an older age compared to their male counterparts. Other factors that could have modulated the performance of surgery as the presence of co-morbidity were not recorded in the database.

The overall incidence of RCC reported in males is approximately 1.6 times higher than in females. Thompson et al, including surgically treated RCCs between 1989 and 2005 (n=1720) found an equal male:female ratio between 40-59 and 60-79 years (1.8:1). In a European multicentre study (n=4774 operated RCCs; 1976 through 2004) the male:female ratio differed in patients ≤40 years (1.2:1) and ≥80 years (1.5:1) from the classical ratio of 2.1:1. A German single centre study of operated RCCs showed similar findings to the current study. The frequencies in males and females were almost equal in patients aged 75 and older.

The conflicting findings presented above could be explained by a better overall survival in women, but also by the different inclusion periods of the studies and by differences in local treatment policies regarding elderly patients. The number of people operated in the eight decade of life is less compared to younger patients for obvious reasons (co-morbidities, less life expectancy). A conservative policy was frequently adopted in older patients before implementation of ablative techniques early 2000 (in the Netherlands from 2003). In our opinion the age categories in our study provide a more even distribution of patients among the groups than the WHO age-based groups and therefore a more sound statistical comparison.

The presence of missing data seems unavoidable in retrospective epidemiological studies. In our study these percentages did not differ from previous published studies on the same subject. Although Aron et al presented a cohort with complete data, this was achieved by excluding approximately 52% of their initially collected data. Missing data on stage and grade was present in 48% of their original data. Woldrich et al reported an equal amount of missing data on stage (13%), subtype (78%) and grade (38%) as in the present study. Therefore not only in our study but also in the precedent ones, a careful interpretation is required when results concerning grade and subtype are regarded. Like others, we can
only extrapolate missing data based on the large sample size.

The relevance of missing subtype remains debatable. Firstly tumours diagnosed as RCC NOS are most likely Clear Cell tumours, considering that the trend in simultaneous decrease in RCC NOS tumours is followed by the most prominent increase in the Clear Cell subtype. Furthermore when adjusting for TNM stage, the different histological subtypes have not been showing significant survival differences. A different matter is the presence of missing grade as Fuhrman grade has shown prognostic value for predicting survival. Despite these findings, grade and subtype are currently not incorporated in the last TNM. If future refinements in prognostic pathological parameters will lead to incorporate grade and subtype to the TNM remains unknown albeit possible.

The age-gender related differences of RCC found in our study might be of clinical consequence. Although millimetre differences in size will not determine the choice of the surgical technique, if women from 41 years onward have less pT3 tumours, they would be more eligible for NSS, contrasting the current tendency of women being treated by RN instead of PN. Conversely the higher incidence of Papillary subtype in men compared to women from 51 years onwards might also prompt the preference of NSS technique over RN, when feasible. If confirmed, the present epidemiological data may play a role in the treatment algorithm of RCC in both genders.

Further research should focus on evaluating outcomes of different treatment policies in elderly patients outside institutional frames and based on wider clinically-based data.

Limitations

The main limitations of this study were the absence of survival data and clinical antecedents that could have been acting as confounders or determinants. The anonymous character of the PALGA database did not permit the retrieval of follow-up data, precluding analysis on survival. Further limitations are the smaller sample of our cohort and the presence of missing data. As commented above, this seems inherent to all retrospective databases and can only be overcome by strict data collection protocols at national level. This limitation, as well as the smaller sample size can be balanced by the fact that our database provided a complete national coverage as opposed to the 26% and 75% nationwide coverage of the US databases used for similar studies. Consequently our data offers a complete picture on trends and gender differences of a decade. A further lesson can be learned when trends in reporting are assessed.

CONCLUSIONS

In an analysis of all operated RCC tumours in the Netherlands an older age in women presenting at surgery for RCC, was only observed in patients over 70 years. The male to female ratio differed with age and was almost equal in patients of 70 years of age and older (1.2:1). Women presented with less pT3 tumours than men from the age of 41 years onward and had significant smaller tumour size only between 51-60 years. Missing data on grade was substantial but diminished significantly between 1995 and 2005.

AKNOWLEDGEMENTS

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