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Small renal cell carcinomas – How dangerous are they really? Results of a large multicenter study

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Abstract ***Aim of the study:*** Modern diagnostic ultrasound and cross-sectional imaging has enabled the detection of increasing numbers of renal tumours. The aim of this study was to investigate the tumour- and patient-specific characteristics and prognosis of small renal cell carcinomas (RCCs) after surgical resection.

Methods: The study included 2197 patients who underwent surgical resection of histologically confirmed RCC $\leqslant$4 cm between 1990 and 2011. Median (mean) follow-up was 56.2 (65.5) months.

Results: At the time of surgery, tumours were staged as pT $\geqslant$ 3a in 175 (8.0%) cases, 134 (6.2%) were poorly differentiated and 75 (3.5%) were metastasised. The larger the tumour size, the higher was the risk of presenting with stage pT $\geqslant$ 3a ($p < 0.001$), poor tumour differentiation ($p = 0.004$), microscopic vascular involvement ($p = 0.001$) and collecting system invasion ($p = 0.03$). The 5-year cancer-specific survival (CSS) rate was 93.8% for stage pT1a versus 79.4% for stage pT $\geqslant$ 3a ($p < 0.001$), and it was 93.7% for G1–2 versus 76.8% for

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G3–4 differentiation ($p < 0.001$). Multivariate analysis identified age in years (hazard ratio (HR) 1.04, $p < 0.001$), metastatic disease (HR 12.5, $p < 0.001$), tumour differentiation (HR 2.8, $p < 0.001$) and non-clear cell histology (HR 0.51, $p = 0.02$) as independent prognosticators for CSS in patients with small RCC. Interestingly, the 5-year cancer-specific mortality rate for pT1a N/M0 patients was 5.8%.

Conclusions: This large multicenter study has clearly shown that, though most small RCC have a low pathological stage and a good prognosis, there is also a small but significant subgroup of these tumours that are already locally advanced or poorly differentiated.

1. Introduction

The introduction and refinement of new imaging techniques like ultrasound and computed tomography during the last decades has substantially increased the number of incidentally detected renal cell carcinoma (RCC), which now accounts for the largest proportion of newly diagnosed renal tumours [1–3]. The majority of small renal neoplasms are low-grade tumours with relatively indolent biological and clinical behaviour [2,4–6]. The aggressiveness of even small RCC may increase with tumour size [4–9], though the published data are not yet conclusive and the influence of primary tumour size on the prognosis is still discussed controversially [10].

Therefore, the aim of this large retrospective multicenter study was to evaluate the prevalence of risk factors such poor tumour differentiation and synchronous metastases in patients with small RCC ($\leqslant$4 cm). Within this group of tumours, we reevaluated the influence of tumour size on established prognostic factors and cancer-specific survival (CSS). We also attempted to assess risk factors for metachronous metastases and subsequent cancer-related death in patients who underwent renal surgery with curative intent for small RCC.

2. Patients and methods

2.1. Patients and tumour characteristics

This study included patients who underwent surgery for histologically proven RCC $\leqslant$4 cm at the Hannover (1995–2006), Marburg (1990–2005), Ulm (1995–2011), Homburg (1990–2008), Mainz (1990–2010) or Jena (1992–2011) University Medical Centers. Histological subtypes were stratified according to the 1997 union internationale contre le cancer (UICC) classification. Staging was based on the 2002 tumour-node-metastasis (TNM) classification. The information on patient and tumour characteristics was obtained from institutional datasets based on a joint protocol. Tumour diameter was determined by each pathologist after macroscopic and microscopic evaluation of each RCC specimen.

2.2. Follow-up

Follow-up was calculated from the date of surgery to the date of death or last follow-up. Death was assessed as either cancer-related or -unrelated. The primary end-point of this study was CSS. Information about the exact date and cause of death for each patient was obtained from hospital records in cases where follow-up or death occurred at one of our institutions.

2.3. Statistical methods

Continuous variables were reported as mean values and standard deviations (SD) for parametric distributions or as median values and interquartile ranges (IQRs) for non-parametric distributions. Chi-square or Fisher's exact tests were conducted to assess correlations of covariate distributions and tumour size subgroups. The *t*-test and analysis of variance (ANOVA) and the Mann–Whitney U test were applied to compare metric variables between two or more subgroups.

Kaplan–Meier estimates of survival time were calculated, and subgroups were compared by the log rank test. Multivariate Cox regression models were used to assess the association between survival and various RCC risk factors. SPSS 19.0 was used for statistical analysis. A two-sided $p < 0.05$ was considered to indicate significance in all tests.

3. Results

Our total population of 2197 RCC patients, 1361 (61.9%) men and 836 (38.1%) women, had a mean (median) age of 61.7 (62.8) years (range, 18–89). Clear cell in 1847 cases (84.4%), papillary in 226 (10.3%), chromophobic in 98 (4.5%) and unclassified histology in 18 cases (0.8%). Radical nephrectomy was performed in 970 (53.8%) and partial nephrectomy in 833 cases (46.2%). Table 1 provides a detailed summary of patient and tumour characteristics.

The total cohort had a median (mean) follow-up of 56.2 (65.5) months (IQR: 25–99), 164 (7.7%) had died of RCC and 232 (10.7%) of other causes.