ELSEVIER

Urologic Oncology: Seminars and Original Investigations 32 (2014) 37.e1–37.e6

UROLOGIC ONCOLOGY

Original article

Preoperative decision making for renal cell carcinoma: Cystic morphology in cross-sectional imaging might predict lower malignant potential

Johannes Huber, M.D., Ph.D.[a,*], Alexandra Winkler[a], Hildegard Jakobi[a], Thomas Bruckner, Ph.D.[b], Wilfried Roth, M.D.[c], Peter Hallscheidt, M.D.[d], Keivan Daneshvar[d], Markus Hohenfellner, M.D.[a], Sascha Pahernik, M.D.[a]

[a] *Department of Urology, University of Heidelberg, Heidelberg, Germany*
[b] *Institute for Medical Biometrics and Informatics, University of Heidelberg, Heidelberg, Germany*
[c] *Institute of Pathology, University of Heidelberg, Heidelberg, Germany*
[d] *Department of Diagnostic and Interventional Radiology, University of Heidelberg, Heidelberg, Germany*

Received 19 December 2012; received in revised form 25 February 2013; accepted 28 February 2013

Abstract

Objectives: Several histologic studies showed more favorable oncologic outcome for renal cell carcinoma (RCC) with cystic change. However, there is no prognostic tool to judge on cystic RCC preoperatively. We hypothesized, that cystic morphology in cross-sectional imaging predicts lower malignant potential.

Materials and methods: From our prospectively conducted oncologic database, we identified 825 patients who underwent surgery for malignant renal tumors between 2001 and 2010. In 348 cases (42%), adequate imaging was available for an independent review by 2 radiologists. We excluded recurrent and synchronous bilateral RCC, familial syndromes, collecting duct carcinoma, and metastases of other origin. For the resulting 319 patients, we compared clinical, pathologic, and survival outcomes.

Results: Median age was 63 (19–88) years and 220 (69%) patients were male. Median follow-up was 1.7 (0–9.8) years. Of 319 renal masses, 277 (86.8%) were solid and 42 (13.2%) were cystic. In cystic RCC, median tumor diameter was lower (3 cm vs. 4 cm, $P = 0.002$) and nephron-sparing surgery was more frequent (69% vs. 41.5%, $P = 0.002$). None of the patients with cystic RCC and 56 (20.2%) with solid RCC had synchronous systemic disease ($P = 0.001$). The nuclear grade of cystic RCC was more favorable ($P = 0.002$). Patients with cystic RCC showed better overall ($P = 0.049$) and cancer-specific survival ($P = 0.027$). In a multivariate model, only synchronous metastases, positive R status, and greater tumor diameter were independent risk factors ($P \leq 0.03$).

Conclusions: We report the first study to show that cystic morphology in cross-sectional imaging might predict RCC with a lower malignant potential. This insight could allow less invasive treatment strategies in selected patients.

Keywords: Renal cell carcinoma; Imaging; Decision making; Prognosis

1. Introduction

Several clinical scores have been developed to support preoperative decision making on treatment strategies for renal masses [1]. These scores aim at integrating all relevant information from imaging studies like tumor size, polarity, location (anterior vs. posterior), shape (exophytic vs. endophytic), centrality, and closeness to the collecting system [1]. However, the tumor's growth pattern (solid vs. cystic) has not been included yet. This preoperative parameter might be of great importance, as the biological features of cystic renal cell carcinoma (RCC) might cause better oncologic outcome [2,3].

Up to 15% of clear cell RCCs show cystic change, and especially papillary RCC type 1 tend to form large cysts [2]. There are several rare histologic variants of cystic RCCs that have been introduced as distinct tumor entities to the 2004 WHO classification [4]. Among these, multilocular cystic RCC (MCRCC) has not been reported to show malignant behavior if a stringent definition is applied [2,5]. However, pathologic and genetic features necessary

* Corresponding author. Tel.: +49 351 45818954; fax: +49 351 4584333.
E-mail address: johannes.huber@uniklinikum-dresden.de (J. Huber).

1078-1439/$ – see front matter
http://dx.doi.org/10.1016/j.urolonc.2013.02.016

for exact classification are not available preoperatively [6,7]. Preoperative imaging provides evidence of macroscopic tumor morphology and some functional aspects like perfusion. For cystic renal tumors, the Bosniak classification provides criteria to assess the share of malignant lesions [8]. But to date, there is no prognostic tool to judge on the oncologic outcome of cystic RCC.

According to previous work [3,6,7,9,10], we hypothesized that cystic RCC had a lower malignant potential than solid RCC. In our cohort study, we used morphologic features from preoperative cross-sectional imaging to identify cystic RCC [11]. Additionally, we performed a pathologic review of all tumors with cystic morphology to determine the share of MCRCCs. This design discloses the prognostic value of preoperative imaging and adjusts for possibly nonmalignant tumors.

2. Materials and methods

The Institutional Review Board of the University of Heidelberg approved the study protocol (Vote S-357/2011). Before including patients in our prospectively conducted oncologic database, we obtained oral and written informed consent from them [12]. From this database we identified 825 patients who underwent surgery for radical nephrectomy (RN) or nephron-sparing surgery (NSS) for malignant tumors at our department between 2001 and 2010.

2.1. Inclusion and exclusion criteria

For inclusion, we required preoperative cross-sectional imaging including a dedicated renal protocol. Adequate imaging was digitally available in 348 of 825 cases (42%), though it was not accessible for a majority of cases from the earlier years of the decade. From these 348 cases, we excluded recurrent and synchronous bilateral RCCs, familial syndromes like von Hippel-Lindau disease, collecting duct carcinoma, and metastases of other origin. Therefore, a total of 29 patients (8.3%) were excluded.

2.2. Definition of cystic RCC

Defining cystic RCC in imaging studies is not congruent with the attribute "cystic" in pathologic evaluation [6,7,10]. With regard to preoperative imaging, we defined cystic RCCs as tumors with a cystic growth pattern and a solid portion occupying a maximum of 25% of tumor volume [6,9,13]. Moreover, it is crucial to differentiate pseudocystic tumors as these necrotic neoplasms typically arise from large solid RCCs [14,15].

2.3. Measurements

Two radiologists (PH and KD) were blinded to clinical data and reviewed preoperative imaging independently. They rated cystic RCC according to the Bosniak classification system [8]. We defined a tumor nodule of at least 5 mm in diameter to represent a solid portion of cystic RCC [11]. We assessed exophytic/endophytic properties following the R.E.N.A.L. nephrometry score [16] and grouped tumor growth to be $\geq$50% exophytic, $<$50% exophytic, and entirely endophytic. The investigators solved diverging judgments consensually. Moreover, we performed a central pathologic review (WR) of all tumors with cystic morphology according to the 2004 WHO classification [4]. Radiologic and pathologic reviews occurred retrospectively.

We recorded age at diagnosis, gender, body mass index (BMI), the Eastern Cooperative Oncology Group (ECOG) performance status, presence of an additional malignancy, tumor diameter, type of surgery (RN vs. NSS), operating time, and year of surgery. Moreover, we reported local R status ("$>$R0" includes Rx, R1, and R2) [17], histologic type, Fuhrman grade, and the tumor node metastasis stage according to the 7th edition [17]. We collected follow-up data from within our institutional aftercare program [12] and scheduled aftercare visits every 3 months for the first 2 years after surgery, every 6 months for the next 3 years, and yearly thereafter. Besides serum chemistry, the examinations included risk-adapted imaging: chest x-ray or thoracic computerized tomography and abdominal sonogram or abdominal cross-sectional imaging.

2.4. Statistics

We presented categorical data by absolute and relative frequencies and used the chi-square test for comparison. We described continuous variables by median and range, and applied the Mann-Whitney U test for explorative univariate statistics. Moreover, we entered variables of oncologic relevance into a multivariate model of logistic regression. We calculated odds ratio, 95% confidence interval, and *P*-value. For estimating overall and cancer-specific survival, we used the Kaplan-Meier method and assessed differences between groups with the log rank test. All tests were 2 tailed with α set at 0.05. We performed all calculations with SPSS statistics 20.0 (IBM, Corp., Armonk, NY).

3. Results

Of 319 renal masses, 277 (86.8%) were solid and 42 (13.2%) were cystic according to preoperative imaging.

3.1. Radiologic findings of cystic RCC

We investigated the 42 cystic RCCs using CT in 10 (24%), MRI in 25 (60%), and both in 7 (17%) patients. Bosniak classification was IIF in 1 (2%), III in 21 (50%), and IV in 20 (48%) tumors. Of 42 cystic RCCs, 6 (14%) were multilocular and 22 (52%) showed a solid portion. There were calcifications in 3 of 17 (18%) CT studies.