

Implication of cystic fluid cytology of renal cell carcinoma on surgical practice

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Abstract

Objectives

To evaluate the incidence of positive cystic fluid cytology and its risk factors in cystic renal cell carcinoma (RCC) addressing its implication on the current surgical practice.

Methods

All clinically diagnosed Bosniak III, IV cystic renal masses from March 2019 to February 2021 were studied prospectively. Database of patients' demographics and cystic tumor characteristics were recorded. Partial or radical nephrectomies were performed by either laparoscopic or robotic approach. Cystic fluid was collected right after specimen retrieval in the surgical field and examined by pathologist. Cytology results were compared to the demographic, perioperative variables using multivariate analysis.

Results

A total of 47 patients of histologically confirmed cystic RCC were included. Partial nephrectomies were performed in 44 patients, while radical nephrectomy in 3 patients. There was no intraoperative cystic rupture or fluid spillage. Positive cystic fluid cytology findings were identified in 28 (59.5%) patients, while negative cystic fluid cytology were identified in 19 (40.5%) cases. Definite malignant cells were observed in 24 patients while the other four patients showed highly suspicious atypical cells. Histologically, 68% of patients were proven clear cell RCC and 85% showed Fuhrman grade 1 or 2 in final histologic review. Univariate and multivariate regression analysis between positive and negative cytology groups showed that the presence of the malignant cells in cystic fluid was significantly associated with patients' age (> 60years) and Bosniak grade of cystic tumor ($p < 0.05$).

Conclusions

Definite malignant cells in cystic fluid cytology were observed through our study. Additionally, patients' age (> 60years) and Bosniak grade are the significant risk factors of positive cytology in cystic RCC. Therefore, necessity of meticulous manipulation of cystic renal tumors, despite their clinical features, should not be underemphasized to avoid the least possible tumor cell seeding in case of cystic rupture when operating such high risk of positive cytology.

Introduction

Cystic renal tumors comprise 5–10% of all renal cell carcinomas (RCC) [1–3]. The risk of fluid spillage and seeding of malignant cells due to cyst rupture is one of the concerns while operating cystic renal

tumors [4–7]. Occurrence of intraoperative rupture of cystic RCC has been addressed in the previous literatures [4, 8, 9].

In retrospective analysis, Pradere et al. reported intraoperative ruptured cystic RCC in 18.7% of 268 patients. None of those had local recurrence or distant metastasis on long-term follow up [8]. Furthermore, laparoscopic fine needle aspiration (FNA) and cystic wall biopsy of cystic RCC did not show any significant oncological consequences [10]. Hayakawa et al. reported that preoperative cystic fluid assessment has shown a positive malignant cytology in only 9–14% of subsequently proved RCC [10, 11].

However, if clinical practice is based on these previous reports, urologists could be less careful during operation of cystic RCC. Consequentially, risk of cystic rupture and the least possible tumor cell seeding could be underestimated. Furthermore, previously published reports were based on preoperative FNA study, which have limitations of inadequate sampling and high false negative rates. Actual presence of malignant cell in cystic fluid and its incidence was not fully evaluated in these previous studies.

Therefore, we prospectively investigated the incidence of positive and negative cystic fluid cytology of histologically confirmed cystic RCC and its risk factors. Our purpose is to precisely assess the actual presence of malignant cells in the cystic fluid of RCC by performing direct cystic fluid aspiration from the retrieved specimen in the surgical field, emphasizing its implication on the current clinical practice.

Materials And Methods

Patient selection

All cystic renal masses diagnosed by abdominal computed tomography (CT) scan were evaluated. Demographic data, cystic tumor size, clinical stage and Bosniak category were collected; along with post-operative histo-cytological results. All patients were evaluated with clinical examination, chest and abdominal CT and renal function test at periodic schedule, with follow up period for 6-32 months.

Inclusion and exclusion criteria

The patients included were those with Bosniak category III and IV on preoperative CT scan. Cystic degeneration tumors were excluded. Cases of insufficient volume of cystic fluid sampling (less than 5 ml) or benign histology found at final pathology were excluded. Cases of polycystic kidney disease were also excluded.

Surgical methods

All surgeries were performed by single high volume surgeon. Surgical methods included laparoscopic partial nephrectomy (LPN), laparoscopic radical nephrectomy (LRN), and robot-assisted partial nephrectomy (RAPN).

Cystic fluid cytology analysis

After specimen retrieval, cystic fluid was aspirated directly from the cysts using 14 Gauge needle in the surgical field. The maximum possible sample volume was obtained. Sample was sent to pathology laboratory for centrifugation for 5 minutes, and supernatant liquid was discarded. Cell pellet and washing solution were mixed, and 10 minutes of second centrifugation was done. After centrifugation, cell pellet and 20 ml washing solution were mixed to make a slide preparation. Prepared slides were stained with Papanicolaou smear. A specialized uro-pathologist performed the cytological study under a high power field light microscope.

Cytological diagnosis was classified into 3 categories of definite malignant cells, atypical cells and negative for malignant cells. Positive cytology, which was defined as the presence of definitive malignant cells or suspicious atypical cells. Malignant cells showed large hyperchromatic nuclei and prominent nucleoli with large abundant cytoplasm which could be clear vacuolated or densely packed. Atypical cells were characterized by dysmorphic nucleus and irregular contour, showing relatively high ratio of nucleus to cytoplasm. Both cells appeared either in clusters or as a couple of scattered single cells of less than 5 cells/HPF in the histological slide (**Figure 1**).

Statistical analysis

The data were analyzed using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, New York, USA). Demographic and perioperative data of each group were compared using Paired t-test. Pearson's chi-square test was used for comparative analysis of two independent cytology group. Univariate and multivariate linear regression analysis were used to determine influential factors of positive cystic fluid cytology. P-value < 0.05 was considered to be statistically significant.

Results

A total of 487 RCC patients underwent surgical resection from March 2019 to February 2021 in our institution. Among them, 51 patients were radiologically diagnosed as cystic renal tumors. Two cases had insufficient fluid sampling, while the other two cases were found to be benign simple cyst or oncocytoma at final histology.

Among the final 47 enrolled patients, 32 were males and 15 were females. Patients' demographics and tumor characteristics of both positive and negative cystic fluid cytology cases are presented in Table 1. Positive cytology was identified in 28 (59.5%) patients. In positive cytology group, cystic mass size ranged from 1.1cm to 14.0 cm with a median of 3.5cm in positive cytology group. Bosniak category III cystic lesions were shown in 9 patients (32.1%) while 19 patients (67.9%) were shown category IV.

Table 1

Patients' demographics and tumor characteristics of cystic renal cell carcinoma cytology (Total number = 42).

Variables	Positive cytology (n = 25)	Negative cytology (n = 17)	P value
Age (years)	52.8 ± 14.3	54.3 ± 13.7	0.738
BMI (kg/m ²)	25.1 ± 5.3	24.2 ± 2.1	0.501
Gender			
Male	16 (64%)	10 (58.8%)	0.742
Female	9 (36%)	7 (41.2%)	
Tumor size (cm)	4.1 ± 2.5	4.0 ± 2.8	0.954
Median tumor size (cm)	3.5	3.8	
Laterality			
Right	11 (44%)	9 (52.9%)	
Left	14 (56%)	8 (47.1%)	
Operation type			
RAPN	19 (76%)	14 (82.4%)	
LPN	4 (16%)	2 (11.7%)	
LRN	2 (8%)	1 (5.9%)	
Bosniak classification			
III	9 (36%)	14 (82.3%)	0.002
IV	16 (64%)	3 (17.7%)	
Clinical stage			
cT1a	13 (52%)	11 (64.7%)	0.053
cT1b	10 (40%)	4 (23.5%)	
cT2a	2 (8%)	2 (11.8%)	

* Values are presented as mean ± standard deviation, or number (percentage).

Abbreviation; BMI: body mass index; RAPN: Robot-assisted partial nephrectomy; LPN: Laparoscopic partial nephrectomy; LRN: Laparoscopic radical nephrectomy.

Variables	Positive cytology (n = 25)	Negative cytology (n = 17)	P value
Histology subtype			
Clear cell	16 (64%)	12 (70.5%)	0.064
Papillary	3 (12%)	2 (11.8%)	
Collecting duct	3 (12%)	1 (5.9%)	
Chromophobe	2 (8%)	2 (11.8%)	
MiT family Xp11.2 translocation	1 (4%)	0	
Histology Grades			
Grade 1	9 (36%)	3 (17.6%)	0.12
Grade 2	12 (48%)	10 (58.8%)	
Grade 3	4 (16%)	4 (23.6%)	
* Values are presented as mean ± standard deviation, or number (percentage).			
Abbreviation; BMI: body mass index; RAPN: Robot-assisted partial nephrectomy; LPN: Laparoscopic partial nephrectomy; LRN: Laparoscopic radical nephrectomy.			

All tumors were operated by minimally invasive surgery. Overall, RAPN and LPN were performed in 35 and 9 patients respectively. Three patients underwent LRN due to central location of the tumor. Neither cystic rupture nor fluid leakage was encountered during surgery or at the time of specimen retrieval.

Gross pathological assessment of the resected masses confirmed the cystic nature of the tumor shown in preoperative CT scan (Fig. 2). In positive cytology group, histological examination revealed clear cell RCC in 18 (64.2%) patients, type 2 papillary variant in 4 (14.2%) patients and collecting duct carcinoma in 3 (10.7%) patients. One lesion of MIT family (Xp11.2) translocation RCC and two chromophobe RCC were identified.

All tumors were graded histologically using Fuhrman grading system. In positive cytology group, grade 1, 2 and 3 were seen in 11 (39.2%), 14 (50%) and 3 (10.8%) of the tumors respectively. None of the patients had grade 4 diseases. Of the 28 positive cytology tumors, 14 (50%) cases were within 4 cm in size (cT1a stage), while 11 (39.2%) were between 4 and 7 cm (staged as cT1b). The negative fluid cytology cysts of the 19 patients showed absence of malignant or atypical cells, but presence of only microscopic macrophages and lymphocytes.

Univariate regression analysis between positive and negative cytology groups showed that the presence of malignant cells in cystic fluid was significantly associated with patients' age (> 60 years) ($p = 0.024$) and Bosniak grade of cystic tumor ($p = 0.002$). However, patients' sex ($p = 0.742$) and tumor size ($p =$

0.528) were not significantly associated with incidence of positive cytology in univariate regression analysis. Also, patients' age (> 60 years) (p = 0.036) and Bosniak grade of cystic tumor (p = 0.002) were significant risk factors of positive cytology. multivariate regression analysis did not show significant association of patients' sex (p = 0.507) and tumor size (p = 0.418) with incidence of positive cytology (Table 2, 3). There was no evidence of local recurrence or distant metastasis on the follow up period.

Table 2
Univariate analysis of risk factors associated with positive and negative cystic fluid cytology groups.

	R²	t	95% CI	P-value
Age (> 60 years)	0.008	0.579	1.26–3.48	0.024*
Gender (male)	0.003	0.331	0.375–1.270	0.742
Tumor size (> 4cm)	0.01	0.636	0.036–1.120	0.528
Bosniak grade	0.209	3.251	1.17–6.731	0.002*
CI: Confidence interval.				
*p < 0.05				

Table 3
Multivariate analysis of risk factors associated with positive and negative cystic fluid cytology groups.

	OR	95% CI	p-value
Age (> 60 years)	1.44	1.406–6.130	0.036
Gender (male)	0.804	0.227–2.847	0.507
Tumor size (> 4cm)	0.952	0.272–3.338	0.418
Bosniak grade	8.296	1.869–32.832	0.002*
OR: Odds ratio, CI: Confidence interval. (R ² = 0.239, p = 0.035)			
*p < 0.05			

Discussion

Cystic RCC represents about 5–10% of all renal cell carcinomas [1–3]. Tumor violation and cancer cell spillage used to be one of concern during surgery, particularly when cystic renal tumors are operated.

Urologists may face vague anxiety if intraoperative cystic RCC rupture is encountered. The stress due to possible tumor cell seeding can adversely affect the surgical and oncological outcomes. However, Pradere et al. reported no local recurrence or distant metastasis on long-term follow up in intraoperative cyst rupture of cystic RCC in 18.7% of 268 patients [8]. Tumorous effect of cystic fluid rupture in cystic RCC has been still on debate, according to previous published reports.

Laparoscopic evaluation with cystic wall biopsy and fluid sampling of 57 indeterminate renal cysts was performed by Limb et al [10]. Eleven patients were diagnosed to have RCC, out of which only one (9%) had positive cystic fluid cytology. There was no peritoneal or port site recurrence on follow up period. Nephron sparing surgery by laparoscopic or robotic approaches for complex renal cysts is safe, feasible and comparable to open or those for solid renal masses [12–15].

Safety of cystic wall puncture for cytology and biopsy during tumor ablation also has been reported in the literature [11–14]. So far, only few reported cases are available of needle tract seeding after percutaneous needle aspiration of renal tumors [16, 17]. However, fine needle aspiration cytology (FNAC) of cystic renal tumor is of limited usefulness, probably due to inadequate sampling and false positive results with low accuracy [18, 19]. Hayakawa and colleagues studied FNAC of renal tumors associated cysts. Positive cytology was identified in only 14% of 37 subsequently proved cystic RCC patients [11]. Meanwhile, the risk of cyst rupture associated with intraoperative manipulations should not be neglected because cyst rupture and subsequent fluid spillage might increase risk of local recurrence [13].

Li et al. have reported 10 positive percutaneous FNAC (48%) of 21 documented RCC after surgery. Among those 11 positive cytology cases, there were 4 cases of suspected malignant and 7 cases of clearly malignant cells [20]. One patient had false positive result of histology proven benign cyst.

However, these previous studies have limitations because they were based on preoperative FNA study. FNAC of cystic renal cancer has limitations due to its inadequate sampling and high false negative rates. Consequentially, risk of cystic rupture and the least possible consequential tumor cell seeding could be underestimated. Up to now, detailed evaluation about the actual presence of malignant cell in cystic fluid cytology and associated risk factor is lacking. Therefore, we prospectively investigated the cystic fluid cytology of histologically confirmed cystic RCC by performing direct cystic fluid aspiration from the retrieved specimen in the surgical field, to figure out the incidence and associated risk factors of malignant cells in the cystic fluid of RCC.

In our data, cystic fluid cytology was positive in 28 (59.5%) of 47 patients including various cell subtypes of RCC, with clear cell type most common. To the best of our knowledge, this is the highest incidence of positive cystic RCC cytology among the previous published in literatures. It may be attributed to the prospective analysis associated with accurate sampling from the specimen in the surgical field, and meticulous handling without cyst rupture. Also, study of cystic fluid cytology in our study revealed definite existence of cancer cells in cystic fluid using light microscope, which warrants meticulous dissection during surgery of cystic RCC to avoid tumor cell seeding caused by cystic rupture. To overcome the hurdles and limitations of inadequate sampling in CT or ultrasonography guided FNAC, we conducted

direct cystic fluid aspiration from the delivered specimen in the surgical field. Furthermore, risk factors of positive cystic fluid cytology have been evaluated through unruptured retrieved specimens.

Of the 28 positive cytology cases, definite malignant cells were identified in 24 patients while the other four cases showed highly suspicious atypical cells. We included atypical cells in the same group of positive malignant cells because they were assumed to exhibit similar tumorous characteristics with malignant cells, due to speculation of their cell components showing dysmorphic nucleus and high nucleus to cytoplasmic ratio. However, actual evaluation of behavior of these cells was limited due to absence of cystic rupture cases.

We presumed that positive cystic cytology would be associated with patient's age (> 60years), Bosniak grade, tumor size (> 4cm in diameter, cT1a between cT1b) or histological grade of the tumor. Among those variables, patients' age and Bosniak grade were found to be the significant risk factors of positive cytology. Twenty-five cases (92%) of positive cytology tumors were less than 7 cm in size (clinical stage T1 disease). Clear cell carcinoma was most common histological subtype and found in 18 patients (64.2%). Both of papillary type 2 variant histology cases were positive for malignant cells. More than two third of these positive cytology tumors were of low Fuhrman Grade 1–2. These parameters' results of positive cytology patients were almost similar to those of the 42 patients included in the study.

The results of our data showed that old age and higher Bosniak grade remained as the significant risk factor of positive cytology in cystic RCC. On the other hand, small tumors of Bosniak class III can still harbor malignant or atypical cells in their cystic fluid.

Although tumor cell seeding of ruptured cystic renal cancer is known to be uncommon in previous published studies, our results still warrant that the necessity of meticulous manipulation of cystic renal tumor should not be underemphasized to avoid cystic rupture in older aged patient (> 60years) and higher Bosniak grade (III, IV). The presence of malignant cells in cystic fluid of RCC could be the evidence that warrants the least possible tumor cell implantation in case of cystic rupture.

Obviously, rupture of cystic component of RCC may lead to spillage of tumor cells in the surgical field. However, the evidence regarding ability of these cells to implant and grow is uncertain yet. This definitely necessitates further studies to understand the biology of this type of tumor cells. Detailed analysis of cystic fluid of renal tumors to understand the biological nature and behavior of the tumor cells is important. Different molecular biomarkers like proteins, interleukines, tumor necrosis and growth factors were observed in the cystic fluid [21, 22]. However, clinical significance of the molecular assay particularly when the malignant cells are absent in the cystic fluid, may worth detailed evaluation.

Chen et al. compared prognosis of patients with intraoperative cyst ruptures group and the group without cyst ruptures among total of 174 patients, through the evaluation of risk factors of intraoperative cystic rupture [23]. There were 27 (15.5%) intraoperative cyst ruptures. The median follow-up time was 60 months. They reported that 5-year recurrence free survival and cancer free survival in patients with cyst rupture were worse than those without cyst rupture. However, there was no significant difference in overall

survival between the two groups. This could be another evidence of tumorous effect of positive cystic fluid cytology when cystic rupture occurred during surgery of cystic RCC.

Main limitations of this study are median-term follow up period and small sample size. Studying the cystic fluid cytology of benign cysts would be helpful to assess the false positive cytology rate to predict the value of FNAC of these tumors. Also, most common histology of our enrolled cases were clear cell type, but a few of other histomorphotypes including papillary type and other cell types are included. As these tumors have different clinical, pathological and genetic features, further studies regarding correlation between cytology findings and each histologic types will be required. Also, due to surgeon's effort and carefulness of not trying to rupture the cystic component of tumor, there was no case of cystic rupture. Paradoxically, actual evaluation of behavior and aggressiveness of these cystic fluid tumor cells was limited due to absence of cystic rupture case.

Conclusions

In the present study, patients' age (> 60years) and higher Bosniak grade (IV) was found to be the significant risk factor of positive cytology in cystic RCC. Therefore, the necessity of meticulous manipulation of cystic renal tumors should not be underemphasized to avoid cystic rupture and the least possible tumor cell seeding in such high risk of cystic RCC cases. To better understand the cystic fluid cells' ability to implant and grow, further cell studies and culture under similar condition and pressure are recommended.

Abbreviations

RCC: renal cell carcinoma; FNAC: fine needle aspiration cytology; LPN: laparoscopic partial nephrectomy; LRN: laparoscopic radical nephrectomy; RAPN: robot-assisted partial nephrectomy; CT: computed tomography

Declarations

Acknowledgements

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Contributions

KJH, QH and SHH developed protocol and project. KJH performed data collection, analysis and management. KJH, QH performed manuscript writing and editing. KJH selected journal and performed writing all drafts including final version of the manuscript. USH, JYL and SHH supervised manuscript writing. All authors reviewed and approved the final manuscript.

Ethics declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board at the institution (Approval number: KC20RISI0357), and is in accordance with Helsinki declaration and its later amendments. Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors have nothing to disclose.

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Availability of data and material

The data that support the findings of this study are strictly available from the corresponding author on reasonable request.

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Figures

Figure 1

Cytology slides of the cystic fluid. (a) Malignant cells, showing prominent and large hyperchromatic nuclei and large abundant cytoplasm which is densely packed. (b) Atypical cells, showing as dysmorphic nucleus with irregular cell contour, and relatively high ratio of nucleus to cytoplasm (N/C) (c) Negative of malignant cell with macrophages and lymphocytes.



Figure 2

Preoperative contrast CT scans of cystic renal tumor and gross picture of retrieved cystic renal cell carcinoma. (a): Bosniak IV renal cyst showing multi-septated cystic mass with enhancing nodular walls. (b): Bosniak IV renal cyst showing gross nodular lesion with multiple septation.