Chapter 9

Renal Cell Carcinoma in End-Stage Renal Disease

Yasukazu Nakanishi, Fumitaka Koga,
Hiroshi Fukushima, Toru Motoi and Ken-ichi Tobisu

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1. Introduction

Acquired cystic disease of the kidney (ACDK) was first described in patients dying from Brights disease by John Simon in 1847 [1]. It was rediscovered and reported in 1977 in a study of 14 kidneys in 30 hemodialysis patients, and six of the 14 patients had renal cell carcinoma (RCC) [2]. Miller et al. subsequently reported a large autopsy series of 155 hemodialysis patients in which ACDK was noted in 58% and RCC in 2% of patients [3].

ACDK must be distinguished from other acquired renal cystic diseases including simple renal cysts that develop as age advances, and the cystic changes found with primary hyperaldosteronism that causes hypokalemia. It must be distinguished from hereditary autosomal-dominant polycystic disease, and from cystic kidney disease such as Von-Hipple-Lindau disease, tuberous sclerosis, medullary cystic disease, autosomal recessive polycystic disease, and medullary sponge kidney [4]. ACDK is defined as the presence of more than three cysts in either or both of the kidneys or the presence of cysts occupying more than 25% of the renal parenchyma in patients with end-stage renal disease (ESRD) [5, 6]. ACDK increases in prevalence and severity with increasing years on dialysis: 20% of patients dialyzed for 1 to 3 years have ACDK, compared with greater than 90% of patients dialyzed for 5 to 10 years [7]. Time spent on hemodialysis is the most important key features of developing ACDK and increasing risk for RCC [8, 9]. The most important predisposing factor for ACDK is a duration of dialysis of 5 to 10 years or longer [6, 10]. Reportedly, the incidence of ACDK in peritoneal dialysis is almost equal to that in hemodialysis patients [11, 12].

In the current practice, periodic screening for RCC is recommended for dialysis patients because of high incidence of RCC. Screening is recommended from the start of hemodialysis. Ultrasonography (US), one of standard screening tools of RCC in dialysis patients, sometimes fails to distinguish RCC from hemorrhagic cysts [13]. The usefulness of magnetic resonance

imaging (MRI) without the use of contrast material has been reported for the detection of RCC in patients with ACDK [14]. The principle treatment strategy for RCC in dialysis patients is radical nephrectomy (RN). Long-term dialysis patients are at high risk for cardiovascular events [4]. Therefore, less invasive surgery is preferable to avoid postoperative systemic complications. Pathologically, clear and papillary RCC had been considered as common histological types of renal cancer arising from acquired cystic disease (ACD) [15, 16]. Recently, a novel standard pathologic entity of ACD-associated RCC has been established [10, 17-19].

In this chapter, we overview the upated topics on RCCs in ESRD patients, particularly focusing on screening and diagnosis, minimally invasive surgery, and pathology.

2. Epidemiology of RCC in hemodialysis patients

Patients with ESRD on dialysis have more than 100 times greater risk of RCC than age-matched healthy controls [20-22]. In a series of 831, 804 dialysis patients followed up for an average of 2. 5 years, 2, 053 (0. 25%) patients were diagnosed as having RCC, representing a 3. 6-fold increased risk over the general population [23]. Kojima et al. reported that in a cohort of 2, 624 patients 81. 8% developed ACDK during a median dialysis time of 11 years and that 1. 68% developed RCC [24]. The risk is considered to be progressively higher in patients with a longer duration of dialysis. According to some recent publications, a long duration of dialysis (> 10y) has a stronger association with ACD-associated RCC than other subtypes of RCC [25-27]. In a multicenter retrospective study by Neuzillet et al. , RCC developing in patients with ESRD has many favorable clinical, pathologic, and outcome features compared with RCC in patients without ESRD.

According to a multicenter retrospective study, more patients diagnosed as having RCC are young and asymptomatic in the ESRD group than the non-ESRD counterpart [28]. Denton et al. reported that of 260 patients who underwent ipsilateral native nephrectomy at the time of transplantation, 11 (4. 2%) diagnosed as RCC with short duration of hemodialysis, and age was significant risk factor of RCC [11]. In ESRD patients, modality of dialysis does not appear to associate with the incidence of RCC; the incidence of RCC is almost same in patients on hemodialysis and those on peritoneal dialysis. Savaji et al. reported the annual incidence of RCC was estimated to be 130 per 100, 000 patients on peritoneal dialysis [29].

3. Imaging studies for screening and diagnosing RCC in ESRD

As mentioned above, ESRD patients are at greatly high risk for developing RCC. In addition, prognosis is better for asymptomatic patients than symptomatic ones among those with ESRD-associated RCC [30]. Since early intervention may prolong cancer free survival [13, 31], periodic imaging studies are considered to be important for detection of RCC in its early stage. Sarasin et al. [32] recommended evaluation strategies with either computed tomography (CT) or US

every three years for all patients on dialysis and annually for those with ACDK. To date, screening for RCC is recommended for ESRD patients.

3. 1. Ultrasonography (US)

Past studies evaluating the prevalence of RCC in patients with ACDK were based on US diagnosis. US is the most widely used screening tool for RCC in patients with ESRD. On US-based screening, RCC was identified in native kidneys in 3. 8% and 3. 9% of ESRD patients of pre- and post-transplantation, respectively [33, 34], which represents a 100-fold increase in prevalence compared to the general population. Gulanikar et al. [33] reported that sensitivity of US screening for the diagnosis of RCC was 36. 3% in ESRD patients.

Because ESRD kidney shows heterogeneous and hyperechoic parenchymal echo-texture and irregular parenchymal contour associated with uneven parenchymal atrophy and compensatory hypertrophy, it would be more difficult to detect RCC on US in ESRD kidneys than in non-ESRD kidneys. Compensatory hypertrophy sometimes produces a mass effect or compresses the pelvo-calyceal systems and thus closely mimics renal neoplasm [35]. US has disadvantage of operator-dependence and often fails to distinguish RCC from hemorrhagic cyst [13].

Among several diagnostic parameters of US, Kim et al. reported the possibility of usefulness of resistive index (RI), which is calculated as (peak systolic velocity – end-diastolic velocity) / peak-systolic velocity on renal Doppler sonography, in detection of RCC in ESRD kidneys. RCC arising in ESRD kidneys shows significantly lower RI values than the background renal parenchyma [36]. Speculated theoretical background is as follows; because tumor vessels generally lack smooth muscle layer, diastolic flow of the tumor vessels is higher than that of the normal vessels, resulting in lower RI values in tumor tissues compared to the non-neoplastic counterparts.

3. 2. Computed Tomography (CT)

Contrast-enhanced computed tomography (CECT) is the most widely used modality for the detection of RCC associated with ACDK (Fig. 1). Takebayashi et al. [37] demonstrated that early enhanced helical CT could detect RCC better than delayed enhanced CT in ESRD patients with and without ACDK because the cortex of the ESRD kidneys shows minimal enhancement in the early phase, rendering higher differences in the attenuation values between the RCC and the atrophic parenchyma. However, as ESRD patients require life-long follow-up, screening with CECT may be burdensome in that it uses ionizing radiation and poses a risk for contrast-induced nephropathy.

3. 2. 1. Bosniak renal cyst classification system

Schwarz et al. [38] recommended a CT-based screening and management protocol in transplant recipients, incorporating the Bosniak Renal Cyst Classification System. The Bosniak renal cyst classification system was initially reported in 1986 based on CT scan findings [39]. The Bosniak system consists of four categories, ranging from simple to complex cysts. Forty-two-59% of category III and 90-100% of category IV lesions were proven to be malignancy [40-42].

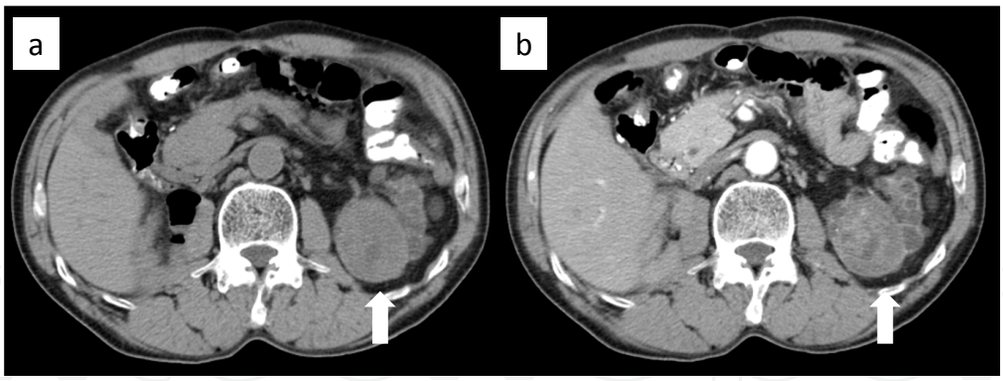

Figure 1. CT images of a 65-year-old man with ACD-associated RCC. a: Unenhancement CT shows multiple small cysts and a mass (arrow). b: At early enhancement phase, the mass (arrow) is slightly and heterogenously enhanced.

Category I. —Simple benign cysts showing homogeneous water content, and a sharp interface with adjacent renal parenchyma, without wall thickening, calcification, or enhancement.

Category II. — Cystic lesions with one or two thin (≤1 mm thick) septations or thin, fine calcification in their walls or septa and hyperdense benign cysts with all the features of category I cysts except for homogeneously high attenuation. A benign category II lesion must be 3 cm or less in diameter and have one quarter of its wall extending outside the kidney, without contrast enhancement.

Category IIF. — Minimally complicated cysts that need follow-up. This group is not well defined by Bosniak originally and consists of lesions that are not classified into category II. There are some suspicious features that deserve follow-up.

Category III. — True indeterminate cystic masses that need surgical evaluation but prove to be benign in many cases. They may show uniform wall thickening, a multilocular nature with multiple enhancing septa, thick or irregular peripheral calcification. Hyperdense lesions that do not fall into category II are classified in this group.

Category IV. —Lesions with uneven or contrast-enhanced thick wall, contrast-enhanced or large nodules in the wall, or clearly solid components in the cystic lesion.

3. 3. Magnetic Resonance Imaging (MRI)

Recently, MRI is one of topics in diagnosis of ESRD-related RCC. Some studies have reported the usefulness of diffusion-weighted MRI in differentiating RCC from benign cyst, without the use of contrast material [43-46]. Diffusion-weighted imaging (DWI) is a non-invasive functional modality using strong bipolar gradients to create a sensitivity of the signal to the thermally-induced Brownian motion of water molecules and in vivo measurement of molecular diffusion [47]. This imaging technique has been applied to the diagnosis of cancer [48]. The apparent diffusion coefficient (ADC) is a quantitative parameter of the degree of diffusion, which is calculated from several DWI images of different *b* values. RCC showed a tendency toward higher signal intensities (SIs) with lower ADC values on DWI obtained at high *b* values than benign cysts (Fig. 2). Akita et al. [14] reported 10 RCCs

containing viable parts in the pathologic specimens showed high signal areas on DWI (at high *b* values). Solitary RCC with no macroscopic degeneration was visualized as a homogenous high SI on DWI and as a homogenous iso SI on T2-weighted image (T2WI). They also reported that the mean ADC of ACD-associated RCCs was lower than the value of clear cell RCCs. Several researchers reported T1-weighted image (T1WI) is useful for discriminating between RCC and hemorrhagic cyst. Hemorrhagic cyst shows homogeneous high SIs or fluid-iron levels on T1WI [13, 49].

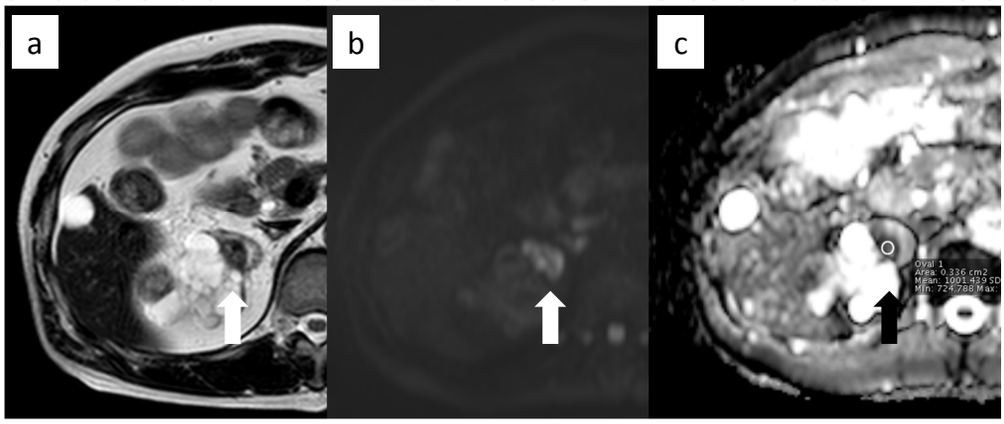

Figure 2. MRI images of a 71-year-old man with ACD-associated RCC. a: Axial T2WI shows a heterogenous signal intensity mass (arrow). b: DWI shows heterogenous high signal intensity mass (arrow). c:ADC map demonstrates the tumor (arrow) with ADC value of 1. 00 $\times 10^{-3}$ mm^2/s.

4. Surgical Treatment

The principle strategy for RCC in dialysis patients is radical nephrectomy (RN). On a nationwide survey in the United States, ESRD-associated RCC patients undergoing RN showed improved survival compared with those not receiving RN [50]. RN is the established surgical approach for conventional RCC. This surgical procedure originally included early vascular control of the renal hilum, removal of the kidney with the Gerota's fascia, removal of the ipsilateral adrenal gland, and a regional lymph node dissection. Although the true benefits of adrenalectomy and regional lymph dissection in patient without enlarged nodes have been a subject of continuing controversy, the principles of early vascular control and removal of the kidney with a wide margin of Gerota's fascia remain the standard of care.

The surgical risk of patients with ESRD is classified as physical status 3 or greater, according to the American Society of Anesthesiologist (ASA) classification [51]. ASA physical status is reported to be a predictor of postoperative outcomes [52]. Therefore, safer and less invasive surgery is recommended for ESRD-associated RCC patients to avoid postoperative systemic complications. Reported series of minimally invasive RN in ESRD patients are listed in Table. 1.

Operation	Authors(publication year)	Number of renal units	Approach		Mean EBL (ml)	Mean OT (min)
			TP	RP		
LRN	Yamashita et al. (2012) [61]	39	1	38	157	240
LRN	Sanli et al. (2010) [62]	20	4	16	111	133
LRN	Bird et al. (2010) [60]	16	16	0	153	unknown
LRN	Ghasemian et al. (2005) [63]	20	20	0	164	390
LRN	Gulati et al. (2003) [59]	6	4	2	120	294
LRN	Iwamura et al.(2001) [58]	6	0	6	58	162
GasLESS	Masuda et al. (2011) [72]	57	0	57	218	170

LRN, laparoscopic radical nephrectomy; GasLESS, gasless laparoendoscopic single-port surgery; TP, transperitoneal; RP, retroperitoneal; EBL, estimated blood loss; OT, operative time.

Table 1. Surgical outcomes of minimally invasive surgery for renal cell carcinoma in ESRD patients.

4. 1. Laparoscopic surgery

Laparoscopic radical nephrectomy (LRN) is a minimally invasive surgical procedure for malignant tumors of the kidney. Clayman et al. first described the successful laparoscopic nephrectomy in 1991 [53]. This was one of the greatest milestones in the history of minimally invasive surgery in that a large solid organ could be removed without an incision of equal or greater size. The utility of the laparoscopic procedures has been verified at many institutions with far less morbidity when compared to open surgery. Many kidney surgeries are currently available laparoscopically [54] via transperitoneal or retroperitoneal approach. Transperitoneal approach has advantages of being a very familiar approach with easily recognizable anatomy and a much larger working space. Some investigators mentioned that advantages of retroperitoneal LRN include quicker access to the renal hilum, easier dissection in obese individuals, the avoidance of intraperitoneal injury, and less interference with respiratoty and hemodynamic functions [55]. In regard to the best approach for performing RN, both retroperitoneal and transperitoneal approaches showed similar oncological outcomes in the two randomized control studies [56, 57]. For RCCs in ESRD patients, LRN also showed feasible and acceptable surgical outcomes [58-62], including bilateral cases [63].

4. 2. Gasless Laparoendoscopic Single-port surgery (GasLESS)

Gasless laparoendoscopic single-port surgery (GasLESS) is gasless (no CO_2 gas insufflation) single-port retroperitoneoscopic surgery that was initiated in the late 1990s in Japan. GasLESS is also referred to as minimum incision endoscopic surgery. Kihara et al. first described GasLESS radical nephrectomy (GasLESS-RN); initially minimum incision of 4 or 5 cm is made on the tip of the 12^{th} rib. The length of incision, which narrowly permits extraction of the kidney

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with perinephric fat, depends on the size of the specimen (Fig. 3). A wide working space is then made through the port by separating anatomical planes extraperitoneally and displacing the peritoneum and the kidney using retractors specialized for GasLESS [64-67]. This operation was certified by the Japanese government as an advanced surgery in 2006, and it has been covered by the Japanese universal health insurance system since 2008. Because of gasless surgery, GasLESS-RN is safely performed for patients with respiratory and circulatory comorbidities compared to LRN. Indeed, feasibility, safety and favorable surgical outcomes of GasLESS-RN were reported for RCC patients [68] [69] including ESRD-associated RCC patients [61, 62]. GasLESS-RN is also indicated for RCC patients on continuous ambulatory peritoneal dialysis because the peritoneum remains intact after GasLESS-RN. Recently, GasLESS-RN incorporates a three-dimentional endoscope and a head mounted display system (3D-HMD system), which enhances safety of surgical procedures and facilitates their fluidity via a coin-sized tiny single port [60] (Fig. 4).

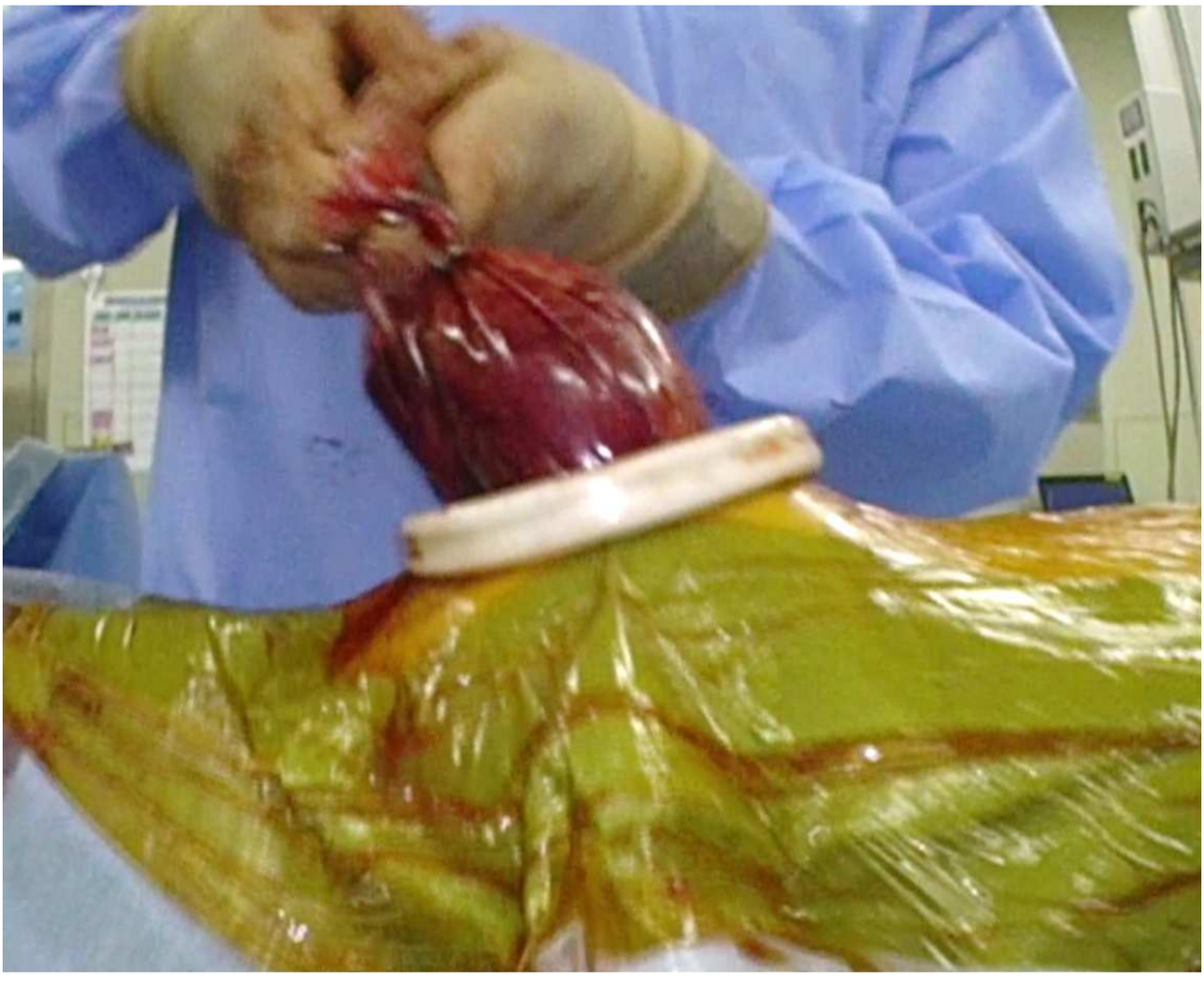

Figure 3. Extraction of a surgical specimen of ACD-associated RCC via a single port in a 65-year-old man treated with GasLESS RN.

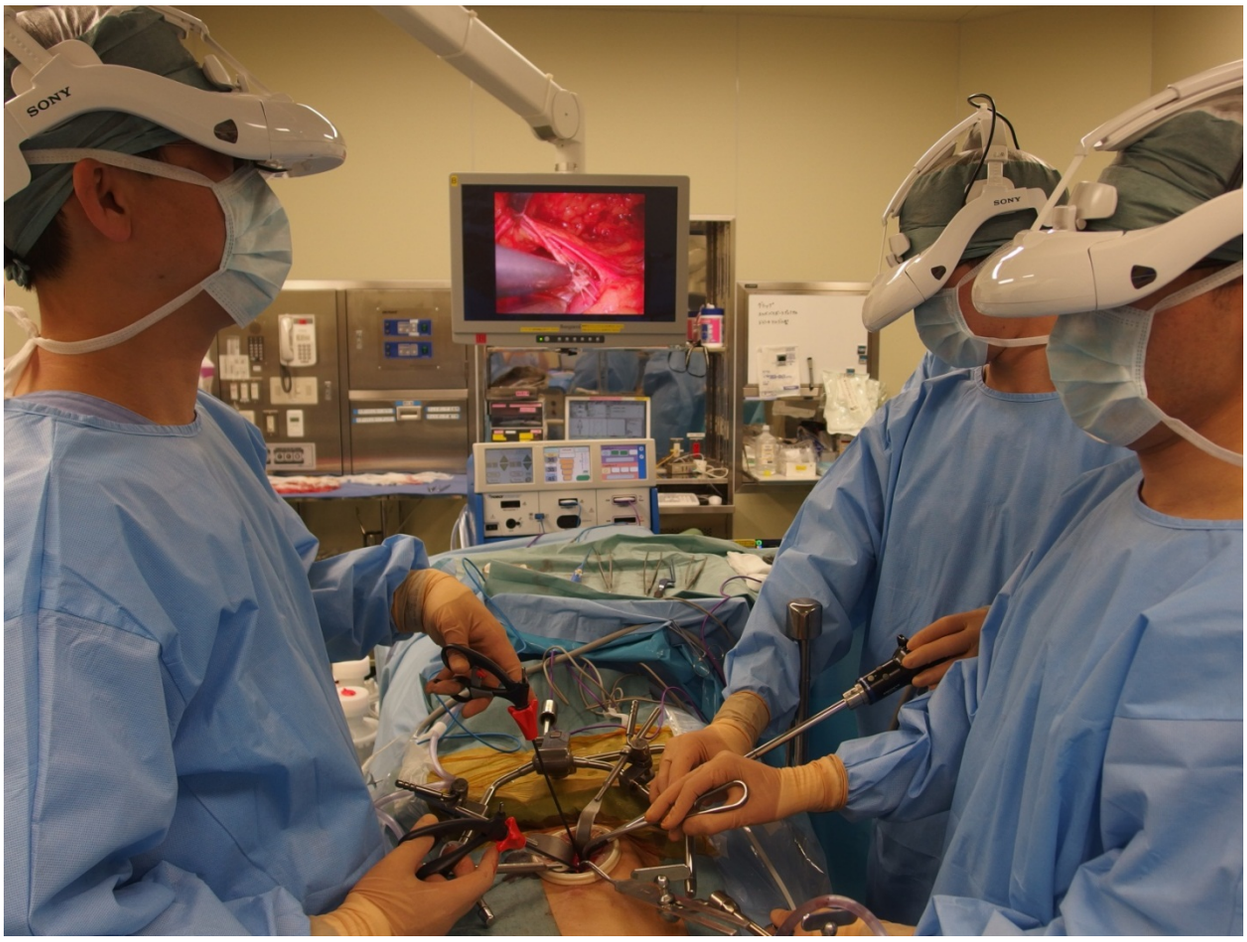

Figure 4. Scenery of GasLESS via a coin-sized port using the 3D-HMD system.

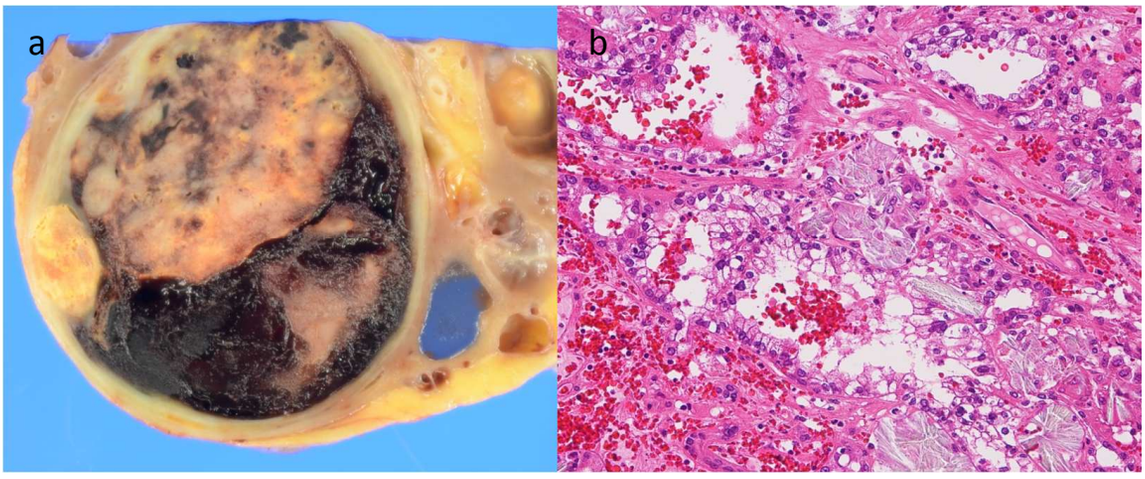

Figure 5. Pathology of ACD-associated RCC in a 65-year-old man. a: Macrophotograph. b: Microphotograph. The tumor tissue contains oxalate crystals.

4. 3. Robotic Radical Nephrectomy

At present, the affirmative opinion for robotic radical nephrectomy has not been published. Hemal et al. [70] reported a prospective comparison of robotic and laparoscopic radical nephrectomy for non-ESRD RCCs. They concluded that there were no benefits of robotic radical nephrectomy observed over LRN for localized RCC.

4. 4. Partial nephrectomy

Partial nephrectomy (PN) is a standard of care for small RCC in patients without ESRD. PN offers better postoperative renal function than RN. RCC in ESRD patients has not yet been reported. However, PN would be beneficial for ESRD patients who have small RCC and still maintain urine production. These patients would have to strictly restrict water intake due to reduced urine output when they undergo RN, which impairs their quality of life. PN might be a viable option for a subset of ESRD patients considering their postoperative quality of life.

5. Pathology

Many investigators had considered for a long time that clear cell or papillary RCC is a common histological type of renal cancer arising from ACDK [15, 16]. However, a new disease entity of ACD-associated RCC showing characteristic histologic features has been established.

5. 1. Characteristics of Histological Types

Papillary RCC was previously reported to be the most common histological subtype found in ACDK in dialysis patients, accounting for 42-71% of cases [15, 17, 71]. Since the establishment of the current histological classification, ACD–associated RCC is the most common histological type of RCC occurring in ESRD kidneys [19]. ACD-associated RCC was found in 36% of surgically resected ESRD kidneys [10]. Some investigators reported that histological patterns of RCC change according to the duration of dialysis. ACD-associated RCC was the major histological subtype in those on dialysis for 10 years or longer [26, 72].

Clear cell (tubulo) papillary RCC was also initially reported in patients with ESRD [10]. However, the majority of cases reported subsequently were not associated with ACDK [73-76]. Reportedly, clear cell papillary RCC comprises less than a few percent of all RCCs [75, 77].

5. 1. 1. ACD-associated RCC

Diagnostic criteria for ACD include the presence of cystic structures occupying at least 25% of the renal parenchyma or greater than three cysts per kidney [78]. ACD-associated RCC appears as a nodule arising from cystic wall, occasionally completely filling the cyst, or as a solid mass separate from the cyst (Fig. 5a). Non-cystic tumors are well circumscribed and may be surrounded by a thick fibrous capsule showing dystrophic calcification. The cut surface of the tumor varies from grey tan to yellowish or brownish and hemorrhage or necrosis is occasionally seen [25]. Multifocality and bilaterality are seen in >50% and >20% of the cases, respectively [10].

Microscopically, ACD-associated RCC is defined as a tumor having eosinophilic or oncocytic cytoplasm and is frequently associated with intratumoral oxalate crystal deposition [10, 17, 79] (Fig. 5b). Some investigators suggest that many microcysts maybe formed by intracytopalsmic vacuoles mainly due to degenerative change. These crystals are multicolored under polarized microscopic observation. Papillary, tubular, cribriform or solid growth pattern may also be seen. Nuclear grade is frequently classified as Fuhrman grade 3 [10, 17, 25]. Clear cell change, sarcomatoid change or rhabdoid features may be present in some cases [10, 80, 81]. Immunohistochemically, neoplastic cells of ACD-associated RCC are positive for α-methyl-acyl-coenzyme A racemase (AMACR), CD10, CD57, GST-α, vinculin and c-met, but negative for cytokeratin 7 (CK7) and high molecular weight cytokeratins [10, 25, 27, 81-83].

5. 1. 2. Clear Cell Papillary RCC

Clear cell papillary RCC is seen in ESRD patients without ACDK. The tumors appear well circumscribed and usually well encapsulated. The cut surface is tan-white to yellow with grossly apparent fibrotic areas and ranges from completely solid to predominantly cystic.

Microscopically, clear cell papillary RCC have variable tubular/acinar, papillary, and cycti-carchitectures [10, 74, 75]. The tumor cells have clear cytoplasm. Nuclear grade is often classified into Fuhrman grade 1 or 2. In contrast to ACD-associated RCC, clear cell papillary RCC is positive for CK7 but negative for AMACR and CD10 [74, 75].

6. Etiology of RCC in ESRD

Genetic profiles are distinct from classic papillary RCC or clear cell RCC. Gain of chromosomes 1, 2, 3, 6, 7, 10, 16, 17 and Y are observed in ACD-associated RCC [81, 82, 84-86]. Deletion of 3p25, +7, -Y are absent in clear cell papillary RCC [74].

The developing process of ACDK and RCC in long dialysis patients is still unclear. Several researchers reported the role of cytokine activation. Phosphorylated c-jun, the activated c-jun, which is a critical component of the AP-1 transcription factors that consist of homo- or heterodimers of basic region-leucine zipper proteins, is positive on staining of atypical hyperplastic cells in ACDK [87]. The concentration such as IL-6, -8, and VEGF is significantly high in the cystic fluid of ACDK [88]. Possibility of the relationship of calcium oxalate crystal and tumorigenesis has also been reported [17, 79, 89]. Immunohistochemical expression of oxidative stress markers, such as iNOS, 8-OHdG, and COX-2, are more frequently observed in ESRD-associated RCC than in conventional RCCs [90], since patients on dialysis are affected by oxidative stress which is caused by an imbalance between the production of reactive oxygen species and the cells ability to neutralize the reactive intermediates [91, 92].

7. Prognosis

ACD-associated RCC patients appearto show relatively good prognosis because of a low incidence of advanced disease [26]. In ACD-associated RCC patients treated with RN,

asymptomatic patients diagnosed on screening show more favorable prognosis than symptomatic patients [30]. Ishikawa et al. reported the actual five year survival rate was 79. 7% and cancer-specific survival rate was 91. 7% for surgically treated 662 cases of ESRD-associated RCC [93]. Neuzillet et al. reported that ESRD-associated RCC seems to exhibit many favorable clinicopathologic features and prognosis compared with conventional RCC [28]. Shrewsberry et al. reported that there was no difference in overall or cancer specific mortality between non-metastatic RCC patients with ESRD and those without ESRD when the patients underwent RN [94]. Several cases of ACD-associated RCC with sarcomatoid change [10] and rhabdoid features [95] have been reported to behave in an aggressive fashion.

8. Conclusions

ESRD patients on dialysis are at high risk for development of RCC. Periodic screening for RCC is recommended for these patients. MRI without use of contrast material would be useful for screening RCC in ESRD patients. ACD-associated RCC and clear cell papillary RCC are the current standard histological spectrum of RCCs arising from the kidney with ESRD. For patients with ESRD-associated RCC in early stage, less invasive surgical treatment is preferable to avoid postoperative systemic complications. Prognosis of ESRD-associated RCC patients is generally favorable when treated in early stage.

Author details

Yasukazu Nakanishi[1], Fumitaka Koga[1*], Hiroshi Fukushima[1], Toru Motoi[2] and Ken-ichi Tobisu[1]

*Address all correspondence to: f-koga@cick. jp

1 Department of Urology, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Honkomagome, Tokyo, Japan

2 Department of Pathology, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Honkomagome, Tokyo, Japan

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