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Renal Cell Carcinoma in Dialysis Patients with End Stage Renal Disease: Focus on Surgery and Pathology

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1. Introduction

In 1977, Dunnill et al. from Oxford at first reported that 14 of 30 dialysis patients with end stage renal disease (ESRD) examined at autopsy had acquired cystic disease of the kidney (ACDK) and that six of these 14 patients had renal cell carcinoma (RCC), including one with distant RCC metastatsis.[1] It is now well established that patients with ESRD are more prone to RCCs with an incidence of approximately 3 to 5 %.[2-5] These studies may misrepresent the true incidence RCC because they primarily relay upon screening radiology, particularly ultrasonography (US), for detection. Better estimate was provided by a single-center study in which most renal transplant patients undergo ipsilateral native nephrectomy at surgery. Based upon strict pathologic criteria reported by Denton et al., prevalence of ACDK, renal adenoma and RCC and oncocytoma were found in 33%, 14%, 4.2% and 0.6% of 260 patients[6], which may be lower than the true incidence given that only one kidney was removed.

Chen et al. found higher incidence of RCCs vs. the general population, with a standardized incidence ratio of RCC in dialysis patients of 24.1 ($p < .01$)[7]. Ishikawa et al. were able to demonstrate that time spent on haemodialysis was the most important risk factor for ACDK and also for the development of RCC. This important observation did highlight the key features of ACDK developing on haemodialysis and apparently increasing the likelihood of RCC[2,8,9]. Hughson's work suggested that during this time there was a progression of cystic lesions from simple to complex or hyperplastic cysts and on to renal tumor formation[10].

A recent nation-wide survey in Japan revealed a 15-fold increase in the number of dialysis patients with RCC in the last 2 decades[8]. Reasons for this rapid increase can be postulated as follows: the increasing number of dialysis patients: the increasing duration of dialysis in these patients: and the prevalence of tumor screening in dialysis patients by imaging studies. The prevalence of ACDK in the haemodialysis population in Japan appears to be higher than that in the USA or Europe and patient survival on dialysis in Japan is significantly longer. These are probably because of different patterns of primary renal disease and reduced cardiovascular comorbidity compared with Western populations[11]. The presence of RCCs also appears to vary within different populations. Kojima's study of 2624

dialysis patients found that 81.8% of their patients had ACDK on a median dialysis time of 11 years with 44 patients (1.68%) of RCCs. This compares with studies from the USA suggesting approximately one-fifth of the 30% or so patients with ACDK will have RCC, therefore close to 6% of the overall dialysis population[5]. This 3- to 4-fold difference in the risk of RCC in ACDK between Japan and the USA may be real or may be a consequence of differences in study populations or of methods used to screen patients.

Dialysis patients with RCC are one of the representative groups of patients with considerable surgical risks. According to the American Society of Anesthesiologists (ASA) classification (http://www.asahq.org/clinical/physicalstatus.htm)[12], surgical risk of patients with chronic renal failure (CRF) is assigned to at least physical status (PS) 3. Dialysis patients often have multiple complications such as respiratory or cardiac problems in addition to CRF. Since the number of RCCs in dialysis patients associated with high surgical risk is also expected to increase, a safe and less invasive radical nephrectomy is warranted.

Laparoscopic radical nephrectomy (LRN) has been used for the management of renal mass in ESRD patients and showed acceptable surgical outcomes[13-16]. Since 1998, we have developed gasless single-port retroperitoneal RN for RCC designated minimum incision endoscopic surgery, MIES[17-19]. This operation is completed via a single port that narrowly permits extraction of the kidney with perinephric fat, without CO_2 gas insufflation, and without injury to the peritoneum[17-19]. This operation was certified as advanced surgery by the Japanese government in 2006, and was covered by the Japanese universal insurance system from April, 2008[18,19]. MIES RN has been shown to be a suitable treatment modality for an expanding spectrum of high risk patients such as RCC in ACDK patients. We already reported the experience of this operation for initial 8 ESRD patients[20] and 7 bilateral cases in ESRD patients[21].

In this context, we will review the recent data about renal neoplasm in ESRD patients including our published papers and recent experiences.

2. Minimum incision endoscopic surgery (MIES) for dialysis patients

2.1 Patients and sources

We reviewed our single-center consecutive cases undergoing MIES RN for RCC in ESRD patients between 1998 and 2009. This database contains information regarding a large number of variables relating to patient characteristics and their surgical procedures. Evaluable parameters included age, gender, side of surgery, duration of dialysis, symptoms, radiological findings, body mass index (BMI) calculated by height and weight, physical status according to the American Society of Anesthesiologists (ASA) scoring system[12]. Time to feeding and walking after the surgery were also recorded.

2.2 Surgical treatment

The surgical technique of MIES RN, was previously demonstrated[17-19]. Briefly, the minimum incision, around 4 to 6 cm depending on the size of the specimen that narrowly permits extraction of the kidney covered with perinephric fat is made obliquely forward following the line of the 12th rib (fig.1). Muscles are separated without cutting and a small space is made under the laterocoronal fascia to allow positioning of a Wound Retractor. After a single port was made, the working space is created by dissecting along the anatomical planes extraperitoneally with long retractors and spatulas under the guidance of both

endoscope and direct vision. The peritoneum is kept intact during the operation. When isolated, the kidney with perinphric fat is put into the pouch (flexible catcher) in the surgical field to prevent rupture of the specimen and extracted through the incision. All procedures are carried out without trocar ports, without gas insufflation and without the insertion of the hands of operators into the operative field. For reducing the bacterial contamination, operative field and subcutaneous space were rinsed with approximately 2000ml and 100ml sterile saline, respectively, before skin closure. Skin is closed by subcuticular suture using polydioxanone, followed by Dermabond. There were no additional dressing or treatment applied postoperatively. Only two inexpensive devices, the wound retractor and the specimen catcher, are disposable in this operation which results in low equipment cost.
The most dialysis patients subject haemodialysis the day before surgery, as well as one day postoperatively, to maintain their routine dialysis schedule. Serum electrolytes were closely monitored, both preoperatively and postoperatively. Patients were discharged home when they met standard discharge criteria and were seen at 1 month, 6 months, 12 months, and at appropriate intervals (relating to their cancer diagnosis and other urological issues) thereafter, in the out-patients clinic for follow-up.

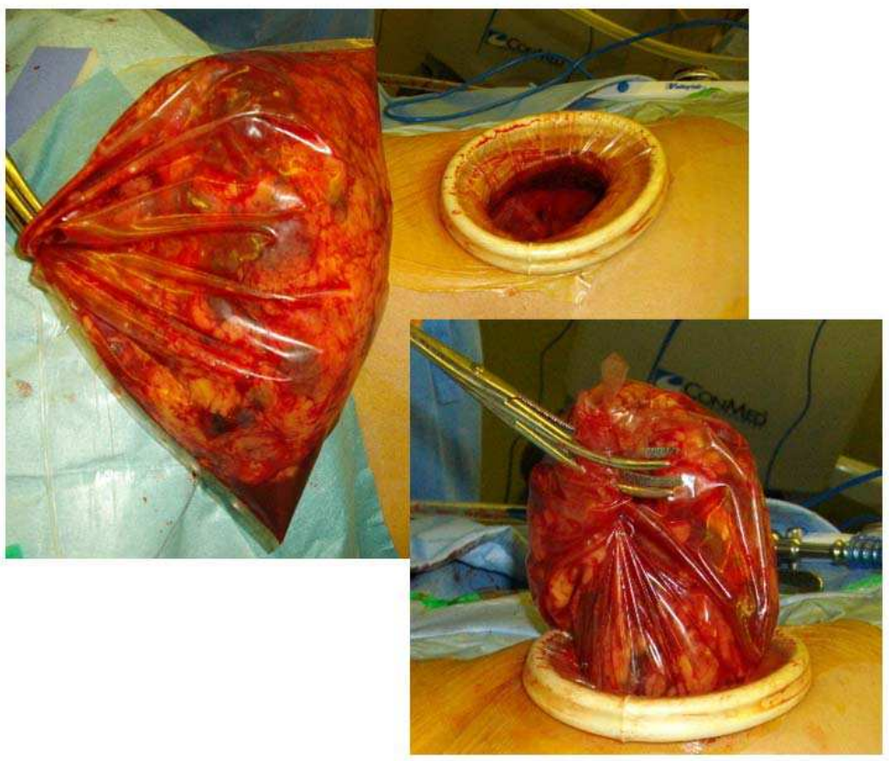

Fig. 1. Resected specimen of ACDK-RCC covered by flexible catcher and 5cm single-port.

2.3 Outcomes of MIES- RN for dialysis patients

We conducted 57 MIES RN for 50 ESRD patients including 7 bilateral RCC cases. For bilateral RCC cases, we have performed sequential operation. When bilateral RCCs are suspected concomitantly, we performed the first RN on the kidney that harbors the larger tumor. After confirming the diagnosis pathologically, the second RN is performed sequentially[21].

MIES RN was successfully completed in all 57 cases with a mean (SD; range) age at RN of 58.6 (10.2; 35-80) years. The mean (SD) operative time was 170 (47) minute with mean (SD) estimated blood loss of 218 (231) cc. The mean (SD; range) length of the extraction incision was 6.1(1.2; 4-9) cm and all kidney specimens with mean (SD) weight of 358 (303) gram were removed intact via single-port. 1 patient required blood transfusion (1.8%). Other complications were not found during operation. The average (SD; range) days to oral feeding and walking were postoperative 1.4 (0.5; 1-3) and 1.3 (0.6; 1-3) days, respectively. Circulatory and respiratory problems did not occur after operation.

Several studies have been performed involving patients with ESRD undergoing laparoscopic RN for RCCs (table.1).

Authors	yr	n	operation	Trans-peritoneal (Renal units)	Retro-peritoneal (Renal units)	Mean EBL (ml)	Mean operative time (min)	Others
Current Study		57	MIES (gasless single-port)[17-19,22]	0	57	218	170	
Bird et al[16]	2009	16	laparoscopic	16	0	153	–	
Reza Ghasemian et al[15]	2005	10	laparoscopic	20 (bilateral)	0	164	390 (bilateral)	
Gulati et al[14]	2003	5	laparoscopic	4	2	120	294	Open conversion in one case
Iwamura et al[13]	2001	6	laparoscopic	0	6	58	162	

Table 1. Summary of minimally invasive radical nephrectomy for RCC patients with ESRD

3. Pathological findings of RCC in dialysis patients

3.1 Characteristics of dialysis patients

We evaluated 57 cases consisting of 43 cases in 38 men and 14 cases in 12 women. Seven bilateral RCC (five men and two women) cases were found. The median (range) duration of dialysis was 12 years (0-27). ACDK was found in 35 patients (70%). On the basis of the duration of dialysis, all cases were classified into four groups: group A, 0-3 years (n=11); group B, 4-10 years (n=15); group C, 11-20 years (n=21) and group D, 21-30 years (n=10).The effects of duration of dialysis on the ACDK state in fig. 2. With increasing duration of dialysis, % proportion of ACDK kidney increased ($p< 0.0001$). Also, univariate and multivariate analysis incorporating into age, gender and duration of dialysis indicated that longer duration of dialysis was an independent predictor of development of ACDK ($p< 0.0001$).

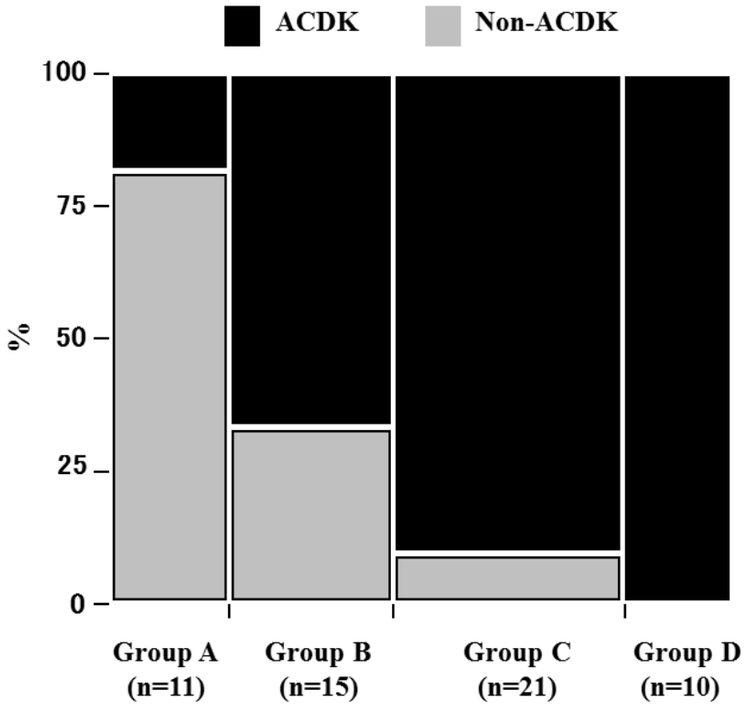

Fig. 2. Transition of proportion of acquired cystic disease of kidney (ACDK) in each group. As the duration of hemodialysis becomes longer, the proportion of ACDK increases ($p < 0.0001$).

3.2 Macroscopic and microscopic findings

There was no correlation between the average size of the tumors and the duration of hemodialysis in all cases. Only in ACDK-RCCs, maximal tumor diameter tend to increase with longer duration of haemodialysis but did not reach to a significant difference ($p=0.09$).

The main tumors and its associated foci (previously categorized according to the WHO 1998 classification system) were re-evaluated histopathologically according to the WHO 2004 classification of renal neoplasms and the 2009 TNM staging classification system (http://www.uicc.org/tnm). Although there is no consensus on the terminology of these special tumors, we used the term of Tickoo *et al*[23]. As a result, the current 57 cases were classified into 32 ACDK-RCCs corresponding to unclassified carcinoma in the current WHO classification, 22 clear cell RCCs and 3 papillary RCCs.

As regards the histological type of the tumors, ACDK-RCCs were more frequent (32/57 lesions, 56.1 %) than clear cell RCCs (22/57 lesions, 38.6%) or papillary RCCs (3/57 lesions, 5.3%). The ratio of ACDK-RCCs in the haemodialysis-related RCCs of each group increased concomitantly with the increase in the duration of haemodialysis; group A, 0/11 (0%); group B, 7/15 (46.7%); group C, 17/21 (81.0%); and group D, 8/10 (80%). Multivariate analysis incorporating into age, gender and duration of dialysis indicated that longer duration of dialysis was an independent predictor of development of ACDK-RCCs ($p < 0.0001$). Male gender also had a tendency to predict ACDK-RCCs but did not reach to a significant difference ($p=0.08$).

ACDK-RCCs had papillary, tubular or tubulocystic structures covered by neoplastic cells with large round or oval to irregularly shaped nuclei with or without prominent nucleoli and eosinophilic granular or focally relatively clear cytoplasms (Figure 3). All of them appeared to develop in close relation to the cystic regions and occasionally showed intratumoral calcium oxalate crystals deposition. Because the above-stated histopathological architecture of ACDK-RCCs was usually absent in conventional RCC, these ACDK-RCCs appeared to be difficult to classify into the known subtypes of RCC.

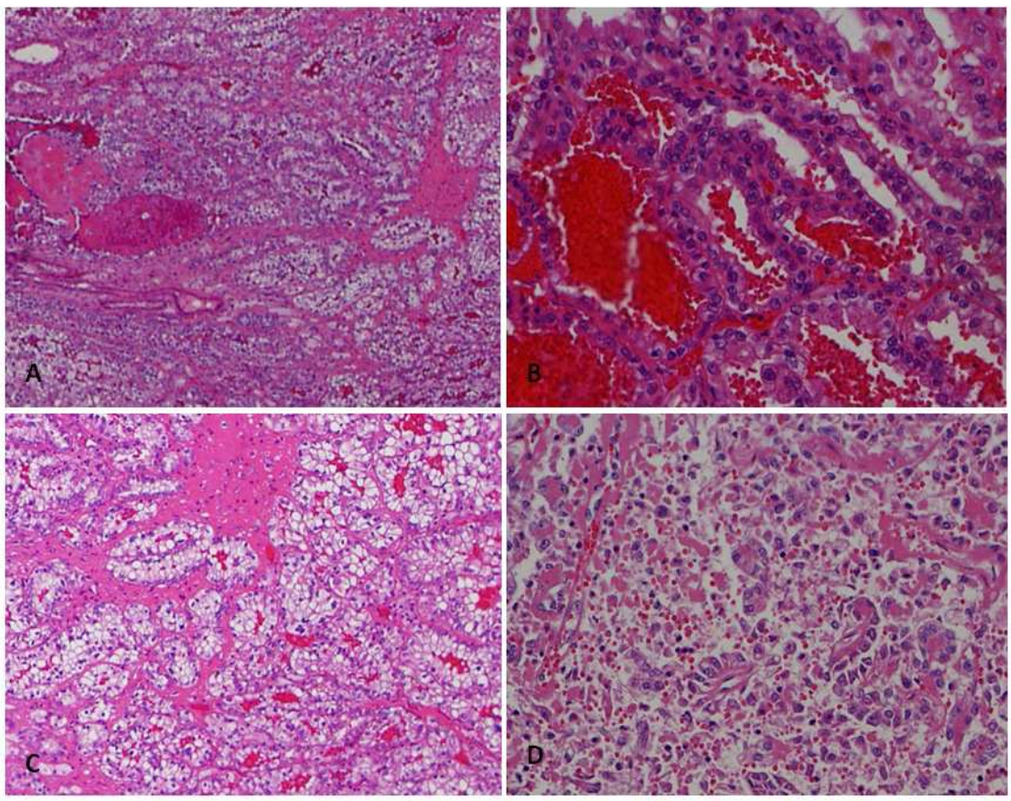

Fig. 3. Acquired cystic disease-associated renal cell carcinoma (ACDK-RCC), the most common tumor identified in ESRD, but only in cases with ACDK. A, This tumor shows a variegated architecture, including papillary, solid, and clear cell like areas. B, The tumor reveals papillary or tubular growth pattern of neoplastic cells with eosinophilic cytoplasms and round nuclei. C, Clear-cell RCC-like areas were focally present. D, ACDK-RCC with sarcomatoid changes were focally present.

3.3 Comparison of ACDK RCCs and non-ACDK RCCs

The mean duration of haemodyalysis was significantly longer in the ACDK-RCC cases (15.9 years) than in the non-ACDK-RCC (clear cell RCC and papillary RCC) cases (6.8 years) ($p < .0001$).There were no significant differences of age, laterality, tumor size, pathological T between two groups. % of male patients tend to be higher in the ACDK-RCC group (85%) than in in the non-ACDK-RCC (63%) ($p=0.07$). Two cases of ACDK-RCCs revealed

aggressive behavior, i.e. death from cancer. Those ACDK-RCCs with aggressive behavior tend to be detected in patients with longer duration of haemodialysis; both cases belonged to group D.

4. Discussion

4.1 Development of ACDK

During the past 20 years, ACDK has become more prevalent as patients with ESRD live longer, undergo more sensitive diagnostic imaging of the kidneys, and are less likely to undergo pretreatment bilateral nephrectomy. ACDK has been defined as macroscopic cystic structures compromising at least 25% of the renal parenchyma or greater than 3 cysts per kidney in a patient in renal failure who was not known to have cysts prior to the onset of renal failure and in whom there is no family history or other evidence of an inherited cystic disease[1]. Of patients on dialysis for less than 3 years 10% to have ACDK, 40% to 60% on dialysis for 3 years have ACDK and more than 90% have ACDK after 5 years on dialysis[24]. The current study also demonstrated that duration of dialysis was closely related with development of ACDK. After three years, proportion of ACDK dramatically increased. Cysts may be found in some patients with renal impairment prior to the initiation of dialysis treatment[25]. Ishikawa et al. reported that when male patients with ESRD were introduced to hemodialysis, the kidney volume was minimized because of the loss of hypertrophied nephrons 3.6 years after the start of haemodyialysis, and thereafter, the kidney enlarged due to the development of ACDK. The maximum kidney volume was obtained at 21.1 years after the start of hemodialysis[9,26]. ACDK may occur less frequently in those who are on peritoneal dialysis and may regress after transplantation[27].

4.2 Incidence of RCC in ESRD patients

the published incidence of RCCs in patients depends on the investigation method (radiologic, surgical, or autopsy). It is well established that patients with ESRD are more prone to kidney neoplasms with an incidence of 4.2% to 5.8%[28]. Those patients with ESRD who also have ACDK are even more prone to the development of carcinoma, with an incidence of 7%[23]. In United States, approximately 20% of those with ACDK will have RCC[5]. In Japan, Terasawa et al.[4], Satoh et al.[29] and Kojima et al.[11] reported 2.6% (41/ 1603), 0.61% (38/6201) and 1.68% (44/2624) of RCC in their patients on hemodialysis,respectively. Such an incidence of RCC appears significantly high, compared with that reported in the general Japanese population where RCC develops in 7.1 of 100000 men and 3.1 of 100000 women, and age-standardized incidence rates per 100 000 population for men and women were 4.9 and 1.8, respectively[30]. In Japan, longer dialysis patients have been dramatically increasing probably because of low cardiovascular comorbidity and low incidence of renal transplantation, leading to development of ACDK and RCC.

4.3 Diagnosis of RCC in ESRD patients

Diagnosis of RCC in dialysis patients may sometimes be difficult because the majority of the RCCs arise from multiple cysts of ACDK and theses RCCs are sometimes not enhanced well in computed tomography. Schwarz et al.[5] recommended a screening and management protocol in transplant recipients, incorporating the the Bosniak Renal Cyst Classification System[31].Complex cystic lesions were defined as those with irregularly thickened cyst walls, hyperdense or nonhomogenic cyst content and/or pronounced intrarenal calcifications,

and/or positive enhancement after intravenous application of contrast media (Bosniak category IIF to III). Ultrasound was followed by computed tomography (CT) scan or magnetic resonance imaging (MRI) when a moderately complex cystic lesion of the kidney was found (Bosniak category IIF) or in case of suspicion of renal cell carcinoma (category III or IV). Importantly, they recommended the nephrectomy in the case of progressive lesions, even if not reaching category III or IV. This is true especially for cystic lesions of category IIF. Fundamentally, we also underwent follow up with ACDK for screening of RCC according to the Bosniak Renal Cyst Classification System. Recently, we introduced diffusion-weighted MRI for detection of ACDK-RCC, which is now under investigation.

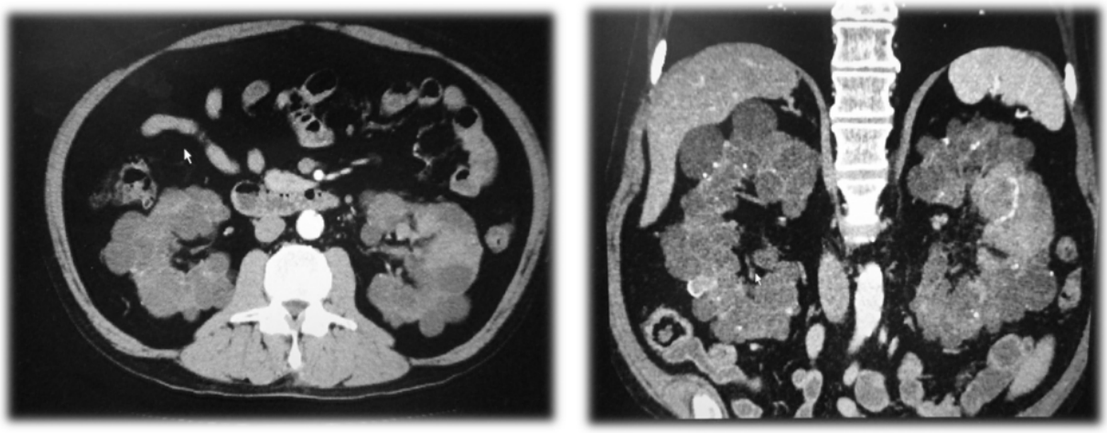

Fig. 4. Multidetector computed tomography for ACDK-RCC. Enhanced mass was found in left kidney (Bosniak category III).

Important problem is, how frequent is multifocality and bilaterality of tumors in ESRD. In the current study, bilateral RCCs were pathologically confirmed in 14% (7/50) of the dialyzed patients. This figure, consistent with previous reports[11,23], is considerably higher than in sporadic RCC in non-dialyzed patients which is reported as being approximately 4%[32]. Ghasemian et al. reported that because of the increased risk of developing RCC in the contralateral kidney, they performed bilateral laparoscopic RN in 10 patients. Of them, 2 patients had bilateral RCC[15]. Kojima et al. reported that satellite RCC nodules were detected in 29.5% of their patients with ACDK, whereas bilateral tumors were present 11.4%. When bilateral RCCs are suspected concomitantly, we performed the first RN on the kidney that harbors the larger tumor. After confirming the diagnosis pathologically, the second RN is performed sequentially[21]. We think that prophylactic nephrectomy should be avoided and followed up by imaging even after unilateral nephrectomy.

4.4 Minimum incision endoscopic surgery, MIES for RCC ; gasless single-port retroperitoneal RN

The perioperative management of ESRD patients is often complex. These patients are at increased risk of postoperative complications secondary to bleeding diathesis, hemodynamic instability, and immunosuppression. They also have higher risk during

anesthesia due to the multiple comorbidities, which include concomitant cardiovascular and respiratory issues. Preparation of the dialysis patient before the operation should include early withdrawal of drugs that affect platelet function, such as aspirin and non-steroidal anti-inflammatory drugs[33]. Preoperative optimization of platelet function and hematologic status may reduce intraoperative bleeding and the need for blood transfusion. Fornara et al. noted an increased transfusion rate in 19-dialysis-dependent patients undergoing laparoscopic nephrectomy (32%) compared with a similar group without renal failure (0%). They attributed this difference, not to increased blood loss or bleeding diatheses, but to a lower initial serum hemoglobin[34]. In our series, only one (1.8%) patients received transfusion. Recently, there were few patients with severe anemia even in ESRD patients by utilizing erythropoietin. Serum electrolytes should be closely monitored, both preoperatively and postoperatively. In addition, patients should not receive excessive amounts of intravenous fluids. Early dialysis may be necessary if serum electrolyte abnormalities or volume overload is present postoperatively.

Laparoscopic radical nephrectomy (LRN) for ESRD patients may offer an acceptable treatment modality with less invasiveness when compared with open RN[35,36]. Despite the several benefits of laparoscopic surgery such as reduced post-operative pain, shorter hospital stay, more rapid return to daily activities and so on, intra-abdominal CO_2 insufflation has various potential risks that may affect the cardiovascular and respiratory system. The pressure effects of pneumoperitoneum decrease cardiac output and stroke volume. The pressure effects also decrease respiratory compliance and increase airway pressure, with possible barotraumas, pneumothorax, and increased intracranial pressure. Gulati et al. reported a case of unexplained hypercarbia and hypotension developed during attempted retroperitoneal LRN requiring termination of the operation[14]. If CO_2 retention is problematic, the intra-abdominal pressure should be reduced and minute ventilation increased. Some have proposed performing laparoscopic procedures using abdominal wall retraction, rather than insufflation, in high-risk patients[37,38]. Bird et al. suggested that insufflation pressure for ESRD patients should be lower as compared with that for that for non-ESRD patients[16].

In patients with prior peritoneal dialysis, significant intra-abdominal adhesions can be encountered. Moreover, transperitoneal surgery itself could result in intraperitoneal adhesion which is not desirable for future peritoneal dialysis for ESRD patients or other abdominal operation. Retroperitoneal LRN approach has been shown to be a safe treatment modality for renal masses in ESRD patients[13].

Venous CO_2 embolism is a recognized risk during laparoscopic procedures. Its clinical presentation ranges from asymptomatic to neurogenic injury, cardiovascular collapse or even death depending on the rate and volume of gas entrapment and patient condition. Venous CO_2 embolism of laparoscopy occurs in 15 per 100,000 cases per year[39,40]. Incidences of subclinical embolism during various laparoscopic procedures have been reported to occur in as much as 6% of nephrectomy cases[41] and 17.1% total prostatectomy cases[42] when transesophageal echocardiography (TEE) was used for monitoring. Serious clinical events related with venous CO_2 embolism have been reported during laparoscopic nephrectomy[43,44] but not during laparoscopic radical prostatectomy. Gas embolism occurred during 2 distinct periods; first, during peritoneal insufflation, and second, during venous complex dissection[45]. Early signs of gas embolism include a rapid drop in end-tidal CO_2 and PaO_2 and an increase in $PaCO_2$ and can be followed by hypotension, hypoxia, cyanosis,

arrhythmia, or cardiac arrest. Elderly or high-risk patients with limited cardiopulmonary reserve might not be able to tolerate these situations.

Based on these above findings, non-use of CO_2 gas and retroperitoneal approach are considered to be key points for lesser invasive surgery for ESRD patients with renal tumors.

In this study, we demonstrated that MIES RN is a feasible treatment for RCC in ESRD patients requiring dialysis. Bleeding and operation time were comparable to LRN, as shown in Table.2. We already reported that this operation has minimal invasiveness similar to that of LRN[17] and an oncological outcome similar to that of open surgery[22]. Operative time and blood loss are similar to those in open surgery and complications including blood transfusion are very rare[17]. Postoperative data, days to oral feeding and days to walking are reported to be equal or sooner compared with LRN[17] and surgical site infection is extreamly rare despite the lack of use of prophylactic antibacterial agents[46]. These findings hold true even in ESRD patients. We stress that this operation has the following advantages over LRN especially for high risk group including ESRD: 1) this operation does not impose circulatory and respiratory stress on ESRD patients and avoids risks of venous embolism, air embolism, and venous thrombosis, which are actually rare, but can be lethal when they occur because of non-use of CO_2 during operation, 2) this operation leaves peritoneal cavity intact, leading no concern about intra-peritoneal adhesion after nephrectomy which is not desirable for possible future peritoneal dialysis and other operations, and 3) this operation can be performed even in patients with a history of intra-peritoneal surgery. In Japan, patients with ACDK-RCC have been increasing now. The cost of disposable instruments in this operation is much lower than that in LRN[47]. Based on these advantages, gasless single-port retroperitoneal RN seems to be ideal minimally invasive surgery for ESRD patients.

4.5 Pathology

In the present study, ACDK development in patients with ESRD/dialysis is associated with a higher risk of RCC and that the duration of dialysis is the main determinant of this risk. Papillary RCC has been previously reported to be the most common histological subtype found in the background of ACDK in dialysis patients, according for 42-71% of cases[28,48]. Our reevaluation showed that ACDK-RCC, but not papillary RCC, was the major histological subtype, accounting for 56.7% tumors in kidneys harbouring ACDK (50% patients), while papillary RCC was found only in 5.3%. Nouh et al. also reported a lower frequency of papillary RCC in dialysis patients (11%)[49].

The present study clearly showed that the histological spectrum of RCC differed according to the duration of dialysis, i.e. conventional clear cell RCC was the predominant subtype in patients with shorter duration of dialysis. Especially, within three 3 years, 91% cases were clear cell RCC, which is similar to histological spectrum of sporadic RCC. On the other hand, ACDK-RCC was the major histological subtype in those on dialysis for ≥ 10 years. These findings were identical to the findings reported by Nouh et al.[49] in Japanese population.

Generally, the biologic behavior of RCCs in ESRD is reported to be less aggressive than the RCCs in sporadic or non-ESRD setting[6,50]. However, some cases have been reported to behave aggressively and metastasize[23,49]. In the present study, two death from cancer were detected. All these two tumors were ACDK-RCC with long term dialysis more than 20 years, which is in line with other reports[23,49].

5. Conclusion

In conclusion, ACDK in patients with ESRD is a potential risk factor for the development of RCC. The risk is further increased by a longer duration of dialysis, which might increase the possibility of developing more aggressive histological subtypes of RCC with an unfavorable prognosis. The spectrum of RCC histological subtypes arising in ESRD is distinct from that of sporadic tumors. We believe that MIES RN, which is completed via a single port that narrowly permits extraction of the kidney with perinephric fat without CO_2 gas insufflation and without injury to the peritoneum, is a feasible treatment option for ESRD patients.

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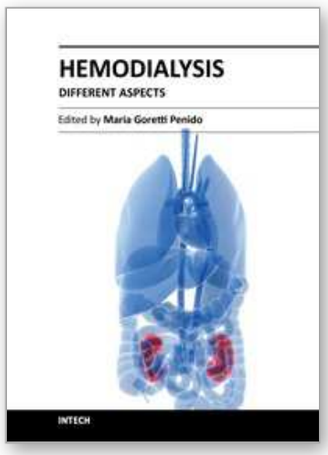

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