

The Piezo Actuator-Driven Pulsed Water Jet System for Minimizing Renal Damage after Off-Clamp Laparoscopic Partial Nephrectomy

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In the setting of partial nephrectomy (PN) for renal cell carcinoma, postoperative renal dysfunction might be caused by surgical procedure. The aim of this study was to clarify the technical safety and renal damage after off-clamp laparoscopic PN (LPN) with a piezo actuator-driven pulsed water jet (ADPJ) system. Eight swine underwent off-clamp LPN with this surgical device, while off-clamp open PN was also performed with radio knife or soft coagulation. The length of the removed kidney was 40 mm, and the renal parenchyma was dissected until the renal calyx became clearly visible. The degree of renal degeneration from the resection surface was compared by Hematoxylin-Eosin staining and immunostaining for 1-methyladenosine, a sensitive marker for the ischemic tissue damage. The mRNA levels of neutrophil gelatinase-associated lipocalin (Ngal), a biomarker for acute kidney injury, were measured by quantitative real-time PCR. Off-clamp LPN with ADPJ system was successfully performed while preserving fine blood vessels and the renal calyx with little bleeding. In contrast to other devices, the resection surface obtained with the ADPJ system showed only marginal degree of ischemic changes. Indeed, the expression level of Ngal mRNA was lower in the resection surface obtained with the ADPJ system than that with soft coagulation ($p = 0.02$). Furthermore, using the excised specimens of renal cell carcinoma, we measured the breaking strength at each site of the human kidney, suggesting the applicability of this ADPJ to clinical trials. In conclusion, off-clamp LPN with the ADPJ system could be safely performed with attenuated renal damage.

Keywords: minimally invasive surgery; new technology; partial nephrectomy; pulsed water jet; renal cell carcinoma
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Introduction

The incidental finding of small renal cell carcinomas have become more common because of the advance of non-invasive diagnostic techniques such as ultrasonography, computed tomography, and magnetic resonance imaging (Pichler et al. 2012; Sugimoto et al. 2013). Partial nephrectomy (PN) has become a gold standard for treatment of small renal cell carcinoma (Sun et al. 2012). Emerging evidence on the relationship between chronic kidney disease (CKD) and life-threatening cardiovascular disease indicates the importance of preserving postoperative renal function in addition to controlling the oncological outcome (Go et al. 2004). Renal hilar clamping, thermal coagulation and ren-

orrhaphy for hemostasis are generally performed in PN (Gill et al. 2002). Decreasing ischemic renal injury has a critical role in reducing postoperative CKD (Mir et al. 2016). In addition, postoperative complications, such as hemorrhage, pseudo aneurysm, and urinary leakage, occur in case of imperfect hemostasis and saturation (Shapiro et al. 2009).

Recently, in this scenario, the off-clamp PN using soft coagulation has been carried (Ota et al. 2014). However, the application of off-clamp PN might depend on the tumor location and surgeon's experience and expertise, and remains challenging because of its massive bleeding. Moreover, the thermal coagulation might end up in postoperative renal damage. Hence, a novel device should be

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required to perform the off-clamp and non-thermal PN.

Water jet technology, based on a conventional pressure-driven continuous method (Oertel et al. 2003, 2004) or a laser (Hirano et al. 2001) method, provides promising results in terms of dissecting tissues. The water jet transmits the kinetic energy to the tissue surface and ejects particles of tissue, creating a corridor through the target tissue, and it can be used for mass reduction. It can selectively dissect tissues with preservation of the blood vessels (minimum 100–200 μm) and nerves, based on the different tensile strengths of tissues against the jet flow (Oertel et al. 2003). Therefore, the water jet technology has been commonly applied to reduce blood loss and parenchymal trauma in liver surgery compared with ultrasonic aspiration or blunt dissection, because liver contains abundant small vessel network (Rau et al. 2008). Another advantage of this technology is the absence of thermal damage that is inevitable with other commercialized instruments.

Although the pressure-driven continuous water jet has been used in surgery since its first application to liver surgery in the 1980s, the excessive water supply and difficulty in device size reduction for introduction into deep, narrow lesions have precluded wider use of this technique. The laser-induced pulsed water jet system was subsequently developed to resolve such issues (Hirano et al. 2003), and it has been reported that the laser-pulsed jets have a significantly increased tumor resection rate, reduced intraoperative bleeding, and reduced operation time in difficult skull base surgery cases in neurosurgery (Ogawa et al. 2011).

A piezoelectric actuator has been developed to replace the laser-pulsed system. We have developed a new piezo actuator-driven pulsed water jet (ADPJ) system that can dissect tissues while preserving fine blood vessels and caus-

ing no thermal injury using this system (Seto et al. 2011). Compared with conventional continuous water jet systems, the ADPJ system offers an intermittent water flow, contributing to dissection at a constant depth and decreases in water volume by combining a quarter quantity of water and air bubbles, which could achieve clearer operative view. These characteristics could be suitable for the laparoscopic surgery.

We had measured the breaking strength of each renal site in the swine, and found that renal capsule or the renal calix had higher breaking strength than renal parenchyma. By setting ADPJ pressure to renal parenchymal intensity, we had already reported the safety of the off-clamp open PN (OPN) using this ADPJ system in swine, without being resected fine blood vessels or renal calix (Yamashita et al. 2014). Thus, the aim of this study was to clarify the safety of the newly developed ADPJ system for laparoscopic PN (LPN) and was to evaluate the renal damage after off-clamp PN using the ADPJ system.

Methods

Laparoscopic ADPJ system and off-clamp LPN in swine

The outlook and an actual photograph of the new laparoscopic ADPJ system are shown in Fig. 1. The piezoelectric actuator is placed at the hand, and the size is 3.5 mm \times 3.5 mm \times 9 mm (Model PSt 150/3.5 \times 3.5/20; Piezomechanik GmbH, Munich, Germany), with a nozzle with an inner diameter of 0.15 mm is attached to the connecting pipe. There was an adjusting point in previous open ADPJ system which occurred an obstruction of the suction tube by the tissue or blood clots. In this new laparoscopic ADPJ system, the outer diameter of the suction tube was improved from 3 mm of open ADPJ system to 4.4 mm. The suction tube tip is a transparent resin pipe, and the state of aspiration can be recognized by surgeon. The pressure of continuous flow from generator was modulated at the

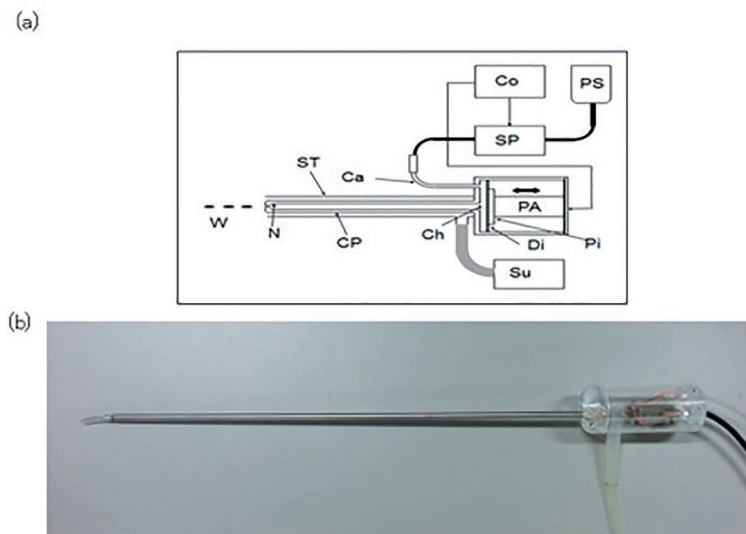


Fig. 1. Piezo actuator-driven pulsed water jet system.

(a) Mechanisms of the ADPJ system. ADPJ, actuator-driven pulsed water jet; Ca, capillary inlet; Ch, chamber; CP, stainless steel connecting pipe; Co, controller; Di, stainless steel diaphragm; N, nozzle; PA, piezo electric actuator; Pi, piston; PS, phosphate saline; SP, supply pump; W, pulsed water; Su, suction pump; ST, suction tube. (b) Photograph of the new ADPJ system. The tip of the nozzle is covered by a suction tube.

pulse jet by activation of the piezo actuator.

Off-clamp LPN with the ADPJ system was performed in eight kidneys. The mean body weight of the swine was 34 kg (27–42 kg). The swine were anesthetized with isoflurane and midazolam, and abdominal air pressure was started up at 8 mmHg. The lower pole outside of the kidney was dissected and the longer axis of the removed kidney was 40 mm. The renal parenchyma was dissected along the mark with the ADPJ system until the renal calyx could be seen. Five milliliters per minute of saline solution was delivered from the tip of the nozzle at a frequency of 400 Hz as pulsed flow. Then, the preserved vessels were coagulated with a bipolar coagulation (SurgiStat II, 30 V, Valley Labs, Boulder, CO) following cutting by scissors. The dissection time and bleeding volume were compared with those of off-clamp OPN with the ADPJ system as in a previous report (Yamashita et al. 2014). After off-clamp LPN with the ADPJ system, residual kidneys were harvested to evaluate morphological features and renal damages. These harvested kidneys were compared with those of off-clamp OPN with a radio knife (SurgiStat II, Valley Labs, 30V) or soft coagulation (VIO 200S system, ERBE Elektromedizin, Tübingen, Germany, effect 7, Max 80 W). The off-clamp OPN was performed with radio knife in four swine and soft coagulation in eight swine. The extent of resection of off-clamp OPN was the same as off-clamp LPN. In addition, the nephrectomy without renal dissection was performed to obtain normal renal tissues in two swine. These experiments were approved by the Animal Experiment Committee of Tohoku University.

Histological evaluation

The harvested kidneys were immediately immersed in 10% neutral buffered formalin solution. Serial 3- μ m-thick sections were prepared, and their morphological features were then examined in paraffin sections with hematoxylin-eosin (HE) staining. The extents of renal ischemia and oxidative stress were examined by immunohistochemical staining for 1-methyladenosine (m1A) that is a transfer RNA-specific modified nucleoside and is highly sensitive to the oxidative tissue damage (Mishima et al. 2014). The monoclonal antibody against m1A was used for early detection of resection surface damage, which is important to evaluate the effect of each surgical device. The kidney was harvested immediately to prevent the tissue degeneration under the influence of renal hilus ligation. Paraffin-embedded sections were incubated with the anti-m1A antibody (1:100), blocked, and then incubated with horseradish peroxidase-labeled anti-mouse IgG; 3,3'-diaminobenzidine (DAB) was used for visualization. Counter staining was performed by hematoxylin. Using the HE and m1A stained tissue sections, the depth of renal degeneration was measured at the deepest point of renal damage.

Expression levels of Ngal mRNA

Approximately 50 mg of tissue was collected from the resection surface and immediately immersed in RNeasy (Qiagen, Chatsworth, CA). Total RNA was extracted from the tissue of resection surface according to the manufacturer's suggested protocol using RNeasy Lipid Tissue Mini Kit (Qiagen GmbH, Hilden, Germany) (Mongroo et al. 2004). Total RNA concentration was determined using a NanoDrop spectrophotometer (NanoDrop Technologies Inc., Wilmington, DE). For each sample tested, the ratio of OD 260/280 was used to provide an estimate of the purity of the nucleic acid, and the ratio in all samples ranged between 1.8 and 2.0. The RNA (1 μ g) was then converted to cDNA with an iScript™ cDNA Synthesis Kit

(Bio-Rad Laboratories, Inc., Hercules, CA). Real-time polymerase chain reaction (PCR) for each sample was performed in duplicate with a Thermal Cycler Dice Real Time System II (Takara Bio Inc., Otsu, Japan). The mRNA levels of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), as an internal control, and neutrophil gelatinase-associated lipocalin (Ngal) were measured. The primer sequences used were GAPDH forward: 5'-CCTTCATTGACCTCCACTACATGGT-3' and reverse: 5'-CCACAACATACGTAGCACCACGATC-3', and Ngal forward: 5'-TTAAGAAATACTCTGGATTGC-3' and reverse: 5'-TACTCTGGTTGTTGGAAAC-3'. The primers are located in separate exons to prevent the amplification of genomic DNA (Kiczak et al. 2013). Relative quantification of targeted gene expression was calculated using the comparative threshold cycle method (Livak and Schmittgen 2001).

Measurement of the breaking strength in human kidney

To examine whether this ADPJ is applicable in the human clinical trials, the breaking strength of each site in the human kidney was measured. The human specimens were collected from the patients who underwent radical nephrectomy for renal cell carcinoma at Tohoku University Hospital. The study was approved by the Ethics Committee of Tohoku University Hospital, and informed consent was obtained from all participants. The breaking strengths of each site in the kidney were measured using a compact table-top universal tester (model EZ-S with force transducer SM-20N-168; Shimadzu Co., Ltd., Kyoto, Japan) according to the previous reports (Seki and Iwamoto 1998; Sato et al. 2013).

Statistical analysis

All values are presented as means \pm standard error of the mean. Statistical analyses and comparisons among groups were carried out using Mann-Whitney *U* test. A probability value of less than 0.05 was considered significant.

Results

Development of laparoscopic ADPJ system and off-clamp LPN in swine

The input voltage of 35 V and 1.5 MPa showed optimal balance between dissection of the renal parenchyma and preservation of small vessels (Fig. 2a) and renal calyx (Fig. 2b), consistent with the pressure for off-clamp OPN in swine (Yamashita et al. 2014).

Only light bleeding was observed at the resection site under the non-hilar clamping condition immediately after the resection, and the suction tube was rarely obstructed by tissues or blood clots. The dissection time was 53 ± 3 minutes, and the estimated blood loss was 124 ± 23 ml, which was significantly less ($p = 0.015$) than that observed in off-clamp OPN conditions (Yamashita et al. 2014).

Histological changes after PN

The depths of renal degeneration using the ADPJ system, radio knife, and soft coagulation were $1,355 \pm 116$ μ m, $3,301 \pm 768$ μ m, and $5,495 \pm 313$ μ m, respectively. The degree of renal damage was significantly less using the ADPJ system than using the soft coagulation ($p < 0.01$) (Fig. 3). Moreover, the ADPJ system and soft coagulation

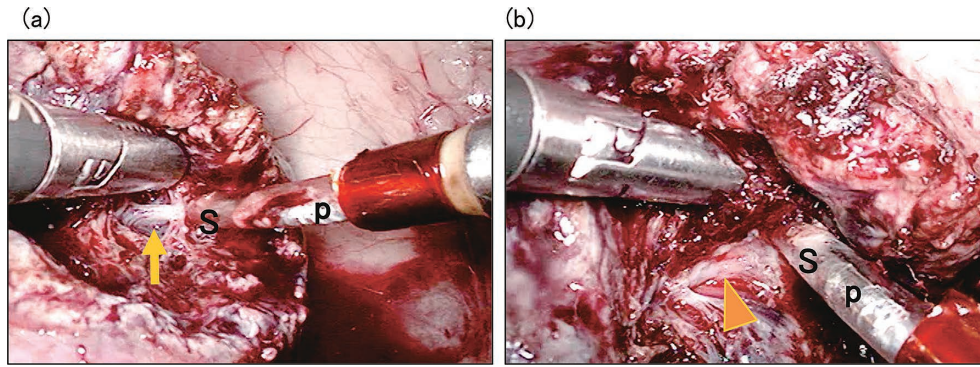


Fig. 2. Operative view of off-clamp laparoscopic partial nephrectomy using the ADPJ system. (a) The piezo ADPJ system can dissect renal parenchyma and preserve small vessels (arrow). P: piezo ADPJ system, S: suction tube. (b) The piezo ADPJ system cannot dissect the renal pelvis (triangle).

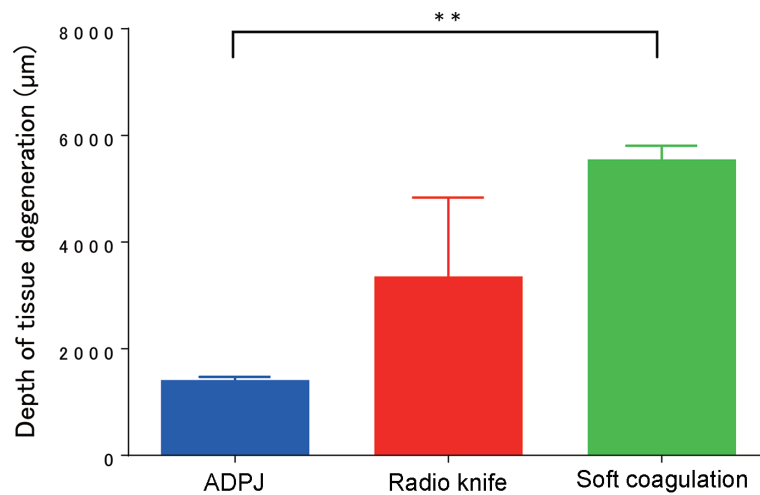


Fig. 3. The depth of postoperative tissue degeneration using each device. The renal degeneration is significantly deeper with the soft coagulation than with the ADPJ system. (** $p < 0.01$, Mann-Whitney U test.)

could control the bleeding from the resection surface after PN, whereas the radio knife could not obtain hemostasis after PN. The HE staining of the renal tissue treated by ADPJ showed interstitial hemorrhage and edema formation due to crush injury at the resection surface, while glomeruli were kept intact (Fig. 4b). These glomeruli did not have an ischemic change or negative staining on m1A, suggesting that ADPJ have a beneficial result to preserve the renal tissues (Fig. 5b). In contrast, broad range of necrosis below the resection surface were observed in the HE staining of the kidney treated by the radio knife and the soft coagulation (Fig. 4c, d). Immunostaining with m1A antibody further revealed that the damaged glomeruli were positive to m1A staining, suggesting that the ischemic change in the glomeruli by the thermal coagulation procedure (Fig. 5c, d).

Expression levels of Ngal mRNA after PN

Ngal is a 25-kDa glycoprotein covalently bound to gelatinase, and it is synthesized and secreted by tubular epithelial cells of the proximal and distal segment in the kid-

ney. It has been reported that Ngal expression was highly upregulated after renal injury and was one of the biomarkers of acute renal injury (Mori and Nakao 2007; McIlroy et al. 2010). The expression level of Ngal mRNA was significantly lower with the ADPJ system than that with the soft coagulation ($p = 0.02$) (Fig. 6). Importantly, the expression level of Ngal mRNA in the renal tissues dissected with ADPJ was similar to that in the normal renal tissues. These data indicate that the ADPJ system has a beneficial effect to protect kidney tissues, compared with the thermal coagulation devices.

Breaking strength of human kidney

The breaking strengths of normal renal capsule and pelvis were higher than that of renal parenchyma. Also, the breaking strength of the pseudo tumor capsule was significantly higher than that of renal parenchyma ($p < 0.01$) (Fig. 7).

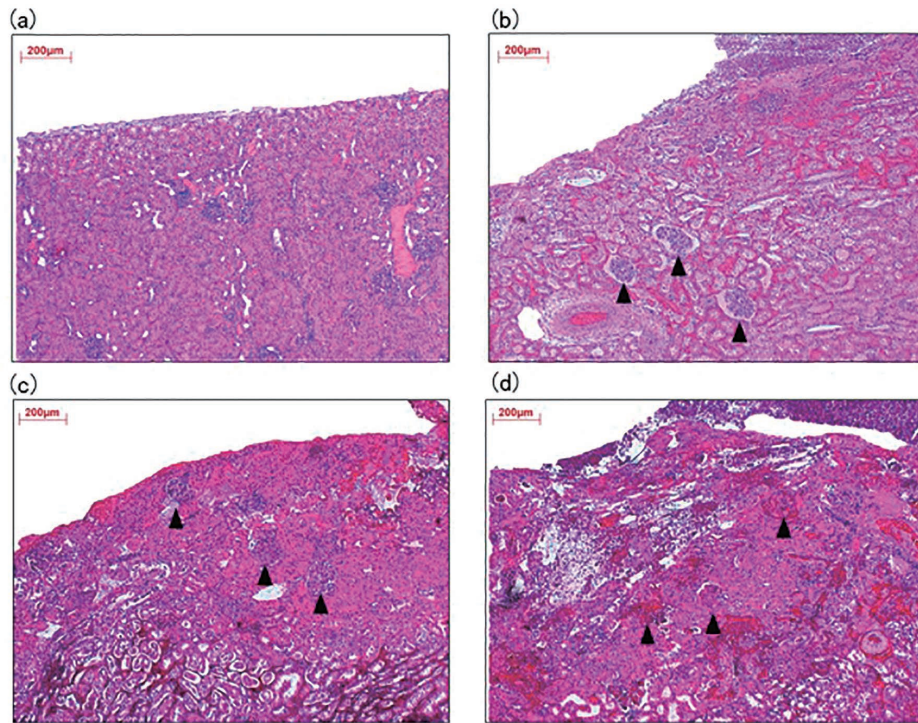


Fig. 4. Hematoxylin-eosin staining of residual kidney.

(a) Normal kidney. (b) Resection surface after partial nephrectomy (PN) using the ADPJ system. Glomeruli are recognized despite existing internal hemorrhage and percolation. (c) Resection surface after PN using the radio knife. Although the form of the glomeruli is retained, there is a broad range of necrosis below the resected margin. (d) Resection surface after PN using the soft coagulation. It is impossible to recognize the form of glomeruli because of broad necrosis, as with a radio knife. ▲: glomeruli. Scale bar indicates 200 μm.

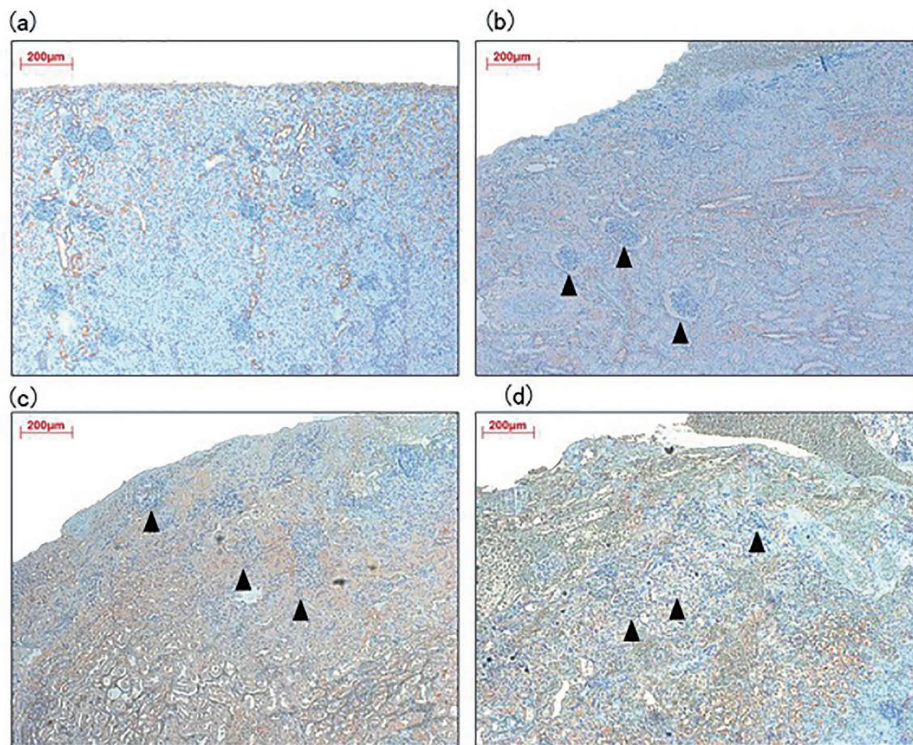


Fig. 5. Immunohistochemical staining of 1-methyladenosine (m1A).

(a) Normal kidney. (b) Resection surface after partial nephrectomy (PN) using the ADPJ system. There is marginal immunoreactivity of m1A due to acute hemorrhage, but there is no apparent ischemic damage because the glomerulus is not stained. (c) Resection surface after PN using the radio knife. Glomeruli recognized on HE are stained with the anti-m1A antibody, reflecting the ischemic injury. (d) Resection surface after PN using the soft coagulation. A broad range of ischemia is present from the resection surface. ▲: glomeruli. Scale bar indicates 200 μm.

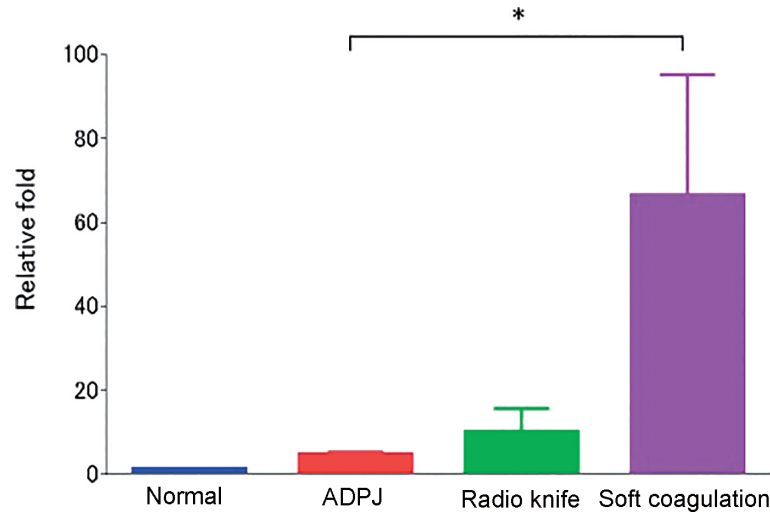


Fig. 6. Neutrophil gelatinase-associated lipocalin (Ngai) mRNA expression in postoperative renal tissues.

The relative expression levels of Ngai mRNA are compared between groups, normalized to GAPDH. The value obtained with the normal renal tissue was used as one arbitrary unit. The expression level of Ngai mRNA was significantly higher in the postoperative renal tissue with the soft coagulation than that with the ADPJ system (* $p = 0.02$, Mann-Whitney U test).

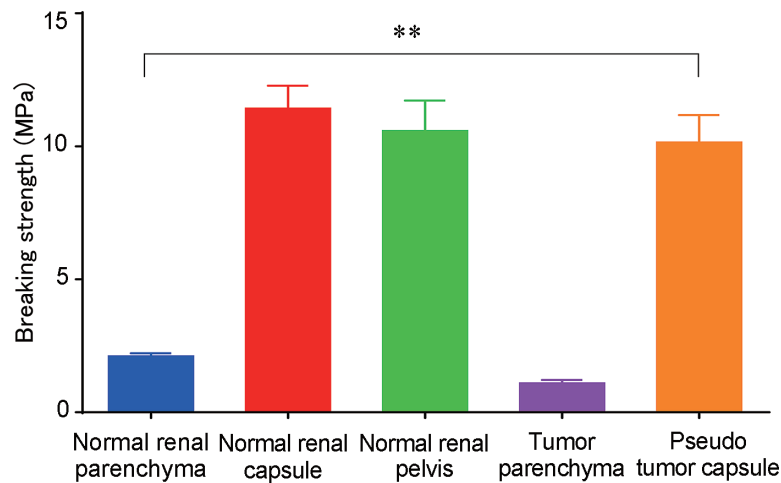


Fig. 7. Breaking strength of human kidney.

The breaking strength was higher in order of normal renal capsule, renal pelvis, pseudo tumor capsule, normal renal parenchyma, and tumor parenchyma. Importantly, the breaking strength of the pseudo tumor capsule was higher than that of renal parenchyma (** $p < 0.01$, Mann-Whitney U test).

Discussion

The primary goal of the treatment for small renal cell carcinoma is improvement of local control of the lesion. However, maximal preservation of postoperative renal function is also important issue to the better outcome for the patients. Many studies have revealed that the amount of residual renal parenchyma after PN is important in predicting future renal function (Kotamarti et al. 2015; Liss et al. 2016). Even though the renal parenchyma was quantitatively preserved by off-clamp PN, it is unclear whether this preserved region really retains the functions, since hilar clamping or thermal coagulation for homeostasis might cause ischemic and necrotic changes in the residual kidney.

Thus, development of a surgical device to achieve a balance between cancer control and postoperative renal function is necessary.

This piezo ADPJ system is a novel surgical device that can achieve these points, namely non-hilar clamping, non-thermal resection, and non-renorrhaphy. By measuring the breaking strength of each renal site beforehand, this device is also able to dissect tissues selectively; for example, the renal parenchyma can be resected without affecting blood vessels or renal pelvis/calyx (Yamashita et al. 2014). Importantly, the ADPJ system offers an intermittent water flow, offering more chance of precise dissection within a certain depth even after prolonged operation than a water jet with continuous flow. Moreover, the water volume is

extremely decreased by combining a quarter quantity of water and air bubbles, which can achieve clearer operative view. These characteristics could be adapted to the laparoscopic surgery, and the optimal conditions of the piezo ADPJ system for off-clamp LPN were established in this study.

This laparoscopic ADPJ system was effective to dissect renal parenchyma easily without damaging the renal pelvis or capsule. The ADPJ system was able to preserve fine blood vessels by tissue selectivity of the water. Unfortunately, this ADPJ system had no hemostatic function, but fine vessels preserved by the ADPJ system could be treated with a hemostatic device reliably. Even if oozing occurred from very fine blood vessels, the oozing could be controlled by abdominal air pressure in laparoscopic surgery. The reason why intraoperative hemorrhage was decreased compared to off-clamp OPN seemed to be reduction of this oozing due to abdominal air pressure (Papp et al. 2003). Moreover, the amount of water was small in consequence of the intermittent water flow, and operators did not need to wipe the camera. This might contribute to reducing both the operator's mental stress and operative time. In addition, the dissection time might be shortened by coagulating and cutting fine blood vessels preserved by the ADPJ system when a bipolar function could be equipped with the ADPJ system.

The immunohistochemical examination of m1A, a tRNA-specific modified nucleoside, showed that the glomeruli of the resection surface operated by an existing thermal coagulation device developed extensive ischemia despite maintaining their appearance on HE staining. Oxidative stress induces direct conformational change in tRNA structure and the change promotes subsequent tRNA fragmentation (Mishima et al. 2014). Such tRNA changes occur much earlier than DNA fragmentation, suggesting that the conformational change in tRNA is a primary response to cell injury. Whereas m1A staining occurred with thermal coagulation devices, there was weak staining of m1A with the ADPJ system, leading to less tissue oxidative damage. Ngal mRNA expression of the resection surface was also significantly lower in the ADPJ group compared with the existing thermal coagulation devices. Although evidence has not yet been obtained for a biomarker of acute renal injury after PN (Mir et al. 2016), Ngal seems to be one of the most reliable biomarkers of renal injury after PN. These results suggest that the ADPJ system might attenuate postoperative renal damage compared with the existing devices.

In this study, the breaking strengths of human kidney were measured for clinical trials. The breaking strength was obviously different between the pseudo tumor capsule and renal parenchyma. If the ADPJ voltage was set to the same intensity of renal parenchyma, the ADPJ system might dissect the renal parenchyma safely, not injured the pseudo tumor capsule. Thus, the ADPJ system was considered to be useful surgical device of PN for the tumor with

pseudo tumor capsule.

The ADPJ system could preserve the renal pelvis, resulting in less postoperative urinoma. If the use of the ADPJ system for off-clamp LPN could reduce the risk of perioperative bleeding, postoperative complications and postoperative CKD, the length of hospitalization and the need of chronic internal use (i.e., antihypertensive agent) might be decreased, thus contributing to reduction of the medical care economy in the treatment for small renal cell carcinoma. However, additional survival experiments should be performed to show the dissection profile and preservation of residual kidney, as well as the long-term effects of surgical manipulation.

There were several limitations in the present study. Firstly, the dissection time and the bleeding volume of off-clamp LPN using the ADPJ system were only compared with data obtained from off-clamp OPN using the ADPJ system. Furthermore, the renal injury of resection surfaces after off-clamp LPN using the ADPJ system was compared with those after off-clamp OPN using radio knife and soft coagulation, because this study was just to produce the prototype of laparoscopic ADPJ system and to confirm the operability, safety and efficacy of this new surgical device. In this study, cavitron ultrasonic surgical aspirator (CUSA, Tyco Healthcare, Mansfield, MA) was not used, which have been widely applied in various regions. CUSA is a surgical device dissecting tissues using tissue selectivity of supersonic vibration, but morphological structure after dissecting the tissues might be different between the ADPJ system and CUSA. Yamada et al. (2014) reported that hepatectomy using the ADPJ system resulted in histologically less injury than the existing radio knife, the ultrasonic surgical system and the ultrasonic cutting shears in swine. The morphological structure after dissecting the liver parenchyma by the ultrasonic surgical system was destroyed, and the blood vessels and bile ducts were not preserved. Secondly, injury of the renal calix was unclear. The breaking strength of the renal calix was significantly higher than the renal parenchyma, and, macroscopically, the injury was not shown intraoperative renal calix. However, whether injured or not, it is necessary to evaluate histologically, and survival experiment should be performed. Thirdly, PN using the existing continuous water jet was not carried out in this study. However, Seto et al. (2011) reported that the dissection characteristics of pulsed jets were superior to those of existing continuous water flows in basic engineering experiments. For clinical trials, the direct comparison between pulsed vs. existing continuous water jet should be performed in the future. Finally, the amount of estimated blood loss might increase in the clinical situation because the blood pressure or intravascular volume was different between human and swine. The ADPJ system, such as an ADPJ system with a bipolar function, should be developed to reduce the amount of estimated blood loss and short the dissection time for the clinical trials in human.

In conclusion, off-clamp LPN with the ADPJ system

could be performed safely. Moreover, the ADPJ system might minimize renal dysfunction caused by ischemia in PN compared with existing devices, contributing to decreased postoperative CKD and improved outcomes after PN.

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Conflict of Interest

Two authors (A.N. and T.T.) received research support for this study from Seiko Epson Co., Ltd. under a collaborative research contract with Tohoku University. Other authors declare no conflict of interest.

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