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Asian Conference on Tumor Ablation guidelines for renal cell carcinoma

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Thermal ablation has been established as an alternative treatment for renal cell carcinoma (RCC) in patients who are poor candidates for surgery. However, while American and European guidelines have been established for American and European patients, respectively, no ablation guidelines for Asian patients with RCCs have been established many years after the Asian Conference on Tumor Ablation (ACTA) had been held. Given that Western guidelines are difficult to apply to Asian patients due to differences in body habitus, economic status, and insurance systems, the current review sought to establish the first version of the ACTA guidelines for treating a RCC with thermal ablation.

Keywords: Carcinoma, renal cell; Cryosurgery; Microwaves; Radiofrequency ablation

INTRODUCTION

Incidental renal cell carcinoma (RCC) has been increasingly detected during ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) for unrelated reasons [1-3]. Moreover, estimates have shown that registered incidences of RCC across China has increased yearly from 1998 to 2008, with the average annual growth rate being 7.89% and males having higher incidences rates than females (8.13% vs. 7.51%, respectively) [4]. According to the cancer registration data of the National Central Cancer Registry of China, approximately 68,300 new RCC cases occurred nationally in 2014, with the crude incidence and mortality rates being 4.99/100,000 and 1.87/100,000, respectively [5].

Although partial or radical nephrectomy has remained the treatment of choice for small RCC, thermal ablation has been considered a plausible alternative treatment given the recent advancements in ablation techniques [6,7]. Since 2000, thermal ablation techniques, such as radiofrequency ablation (RFA), cryoablation, and microwave ablation (MWA), have become increasingly available in clinical practice and utilized as the main treatment modalities. These minimally invasive treatments have been established as excellent alternatives to surgery among American [8] or European [9] patients. However, ablation guidelines for Asian patients with RCC have yet to be been established despite the Asian Conference on Tumor Ablation (ACTA) having been held for quite some time. Therefore, the ACTA committee had been tasked to create guidelines for ablation. The current review aimed to establish the first version of the ACTA guidelines for treating RCC with thermal ablation.

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METHODS

These guidelines did not need approval of Institutional review board because it is a review article. Thus, written informed consent was not necessary. Three radiologists (BKP, SHS, MF) and one urologist (YW), who came from Asian countries including Korea, Taiwan, Japan, and China, were the key members in the guideline ACTA committee for renal tumor ablation. They developed the key questions and discussed each guideline. Renal tumor ablation guidelines were built up after they reviewed many investigations including randomized controlled studies, meta-analyses, case-control studies, expert opinions, and case series. Finally, each guideline was built by means of consensus agreement after it was discussed based on literatures review and our experiences. The levels of recommendations were graded as A, B, C, and D according to the guidelines [10]. The key questions were described in the Table 1 [10]. Recommendation A is defined when there is a clear rationale with multiple randomized controlled trials that can be generalized because they have sufficient test or meta-analysis results supports a recommendation [10]. Recommendation B is defined when there is a reliable basis with reasonable grounds supporting this through well-performed cohort studies or patient – control group studies [10]. Recommendation C is defined when there is a possible basis with relevant grounds which are seen through randomized clinical studies or case reports and observational studies carried out in a small institution, despite their inherent unreliability [10]. Recommendation D is defined as expert opinions in which there is no basis to support the recommendation, but they are supported by expert opinion or expert clinical experience [10].

1. Pre-ablation considerations

1) Treatment indications

The American Urological Association (AUA) and European Association of Urology (EAU) recommend partial or radical nephrectomy as the treatment of choice and consider thermal ablation a secondary treatment option for patients with RCC [6,7], mainly due to the lacking of strong evidence in support of replacing partial nephrectomy. Although several investigations [11-17], have shown that thermal ablation has potential as a primary treatment for RCC, such studies were not randomized controlled trials. Therefore, evidence-based studies demonstrating that thermal ablation is not inferior to nephrectomy in terms of oncologic outcomes are needed.

Despite the lack of evidence, the AUA and EAU recommend ablation therapy as the primary treatment for patients who are poor surgical candidates due to increased risk for postoperative morbidity [6,7]. Such clinical characteristics consist of impaired cardiopulmonary function, chronic liver disease, chronic kidney disease, prolonged bleeding time, deficient coagulation factors, and other severe co-existing morbidities. Moreover, studies have shown that ablation therapy can be a good alternative for treating hereditary RCC [18,19], single kidney RCC [12,20,21], central RCC [15,22,23], and recurrent RCCs [24-26]. While no absolute contraindications

Table 1. Key questions and recommendation levels in renal tumor ablation guidelines

Key question	Recommended guideline	Recommendation level
What are indications in treating an RCC?	Patients with high risk of post-operative morbidity	B
What is the role of pre-ablation imaging?	Making a treatment planning	B
What are patients' preparations prior to ablation therapy?	NPO and stable laboratory findings	B
What type of anesthesia is recommended in each ablation?	Conscious sedation, monitored anesthesia care, or general anesthesia	B
What are prevention methods to avoid thermal damage?	Position change, levering applicator, or hydrodissection	B
Is renal mass biopsy necessary prior to thermal ablation?	Biopsy is mandatory to avoid a benign tumor.	B
What ablation modality is chosen in treating an RCC?	Small RCC (<3 cm) can be treated with all types of ablations. Cryoablation and microwave is recommended to treat large RCC (>3 cm).	C
What imaging modality is chosen in guiding ablations?	CT is the best modality, but US can be used for treating exophytic RCC.	B
Is thermal ablation useful in treating a cystic renal mass?	Thermal ablation is useful for treating cystic renal mass.	B
What are the protocols, complications, and outcomes?	See the details in the section of thermal ablation modalities.	B
How or when should patients be followed?	Every 6 months within 2 years and once a year until 5 years	B
How does thermal ablation influence renal function?	Many tumor factors involved in affecting renal function change.	B

RCC, renal cell carcinoma; NPO, nil per os.

exist for thermal ablation, relative contraindications include fever, severe coagulopathy, and severe bleeding tendencies. However, thermal ablation can be performed granted that these conditions are addressed. Prior to thermal ablation, fever should be assessed and controlled. Moreover, the platelet count should not fall below 50,000, while the internalized normalized ratio should exceed 1.5 [27].

2) Pre-ablation imaging for planning

Pre-ablation imaging is important for establishing treatment plans given that it allows for lesion detection and characterization, lesion localization, lesion approach determination, and prevention of complications [8,9]. Considering that pre-ablation imaging increases medical cost and radiation exposure [28,29], carefully balancing the effectiveness, and hazards of pre-ablation imaging when managing patients with RCC is imperative. Numerous interventional radiologists prefer using CT guidance for thermal ablation given its shorter scan time, lower medical cost, fewer imaging artifacts, and increased availability [8,9,30]. However, MRI should be considered in pediatric or pregnant patients, as well as those sensitive to iodine contrast material. While US is generally useful in detecting or characterizing renal mass, this modality cannot replace CT or MRI given its inability to guide pre-ablation planning as stated earlier.

3) Patient preparations

Pre-ablation CT or MR images should be carefully assessed to determine the appropriate approach for RCC, type of thermal ablation technique, patient positioning during ablation procedures, and prevention of thermal injury to neighboring organs [31].

Patients should fast more than 6 hours before ablation therapy given that risk for aspiration when non-fasted patients vomit during ablation procedures [15,32]. Furthermore, fasting is necessary considering that interventional oncologists need to prepare for emergency arterial embolization, percutaneous nephrostomy, or ureter catheterization when intractable bleeding or hematuria, irreversible ureter obstruction, or uncontrolled urine leakage occur during ablation procedures.

Urethra catheterization prior to ablation is recommended for measuring the amount of excreted urine or detecting gross hematuria [31,33,34]. Antibiotic treatment may not be necessary when sterile techniques had been maintained during ablation [33,34].

4) Types of anesthesia

Conscious sedation or monitored anesthesia care has been frequently utilized during cryoablation given that most patients can tolerate the pain associated with the procedures [30,35]. However, general anesthesia is strongly recommended during RFA or MWA considering that these procedures evoke more severe pain [36,37]. However, the type of anesthesia should be selected based on the clinical situation. Regardless of the ablation modality used, general anesthesia is useful for patients who cannot remain in a specific position for 2 hours or more [30,32]. Furthermore, general anesthesia is mandatory when treating RCC abutting the adrenal gland or sympathetic chain due to frequent hypertensive crisis [27]. An arterial or central line should be secured prior to thermal ablation for continuous blood pressure monitoring given that intermittent blood pressure measurements can create difficulties during immediate intervention in patients with hypertensive crisis or a hypovolemic shock.

5) Preventing complications

Ureter catheterization and pyeloperfusion are recommend to reduce thermal damage to the urothelium when treating RCC close to the ureteropelvic junction [8,31,38,39]. Hydrodissection is also recommended to avoid thermal damage to the small or large bowel when the RCC-to-bowel distance is below 0.5 cm (Fig. 1) [8,31,40]. However, the safe distance should be adjusted considering that the size of the ablation area depends on the degree of tissue perfusion [41], type of thermal ablation [8,31,40,42], and neighboring organs [43]. As such, interventional oncologists should carefully monitor the growth of the ablation area during thermal ablation. Notably, the size of the ablation margins is much easier to determine with cryoablation than with RFA or MWA during CT-guided procedures.

6) Renal mass biopsy

Percutaneous biopsy is mandatory to avoid unnecessary treatment for benign tumors [8,9], including angiomyolipoma and oncocytoma, which have been histologically detected among incidental renal masses [44,45]. Moreover, determining the subtypes of RCC or metastasis can be useful for further management after thermal ablation. Therefore, thermal ablation should not be performed without histologic confirmation of RCC. Repeat biopsy is recommended in cases of non-diagnostic biopsy results [46]. US has been frequently preferred for renal mass biopsy guidance given that Asian patients tend to have lower body mass indices than Western patients [3,47,48]. However, CT is recommended for the biopsy of RCCs that are inaccessible under US guidance. Renal mass biopsy should not be performed on the same day as thermal ablation considering that precise diagnosis requires

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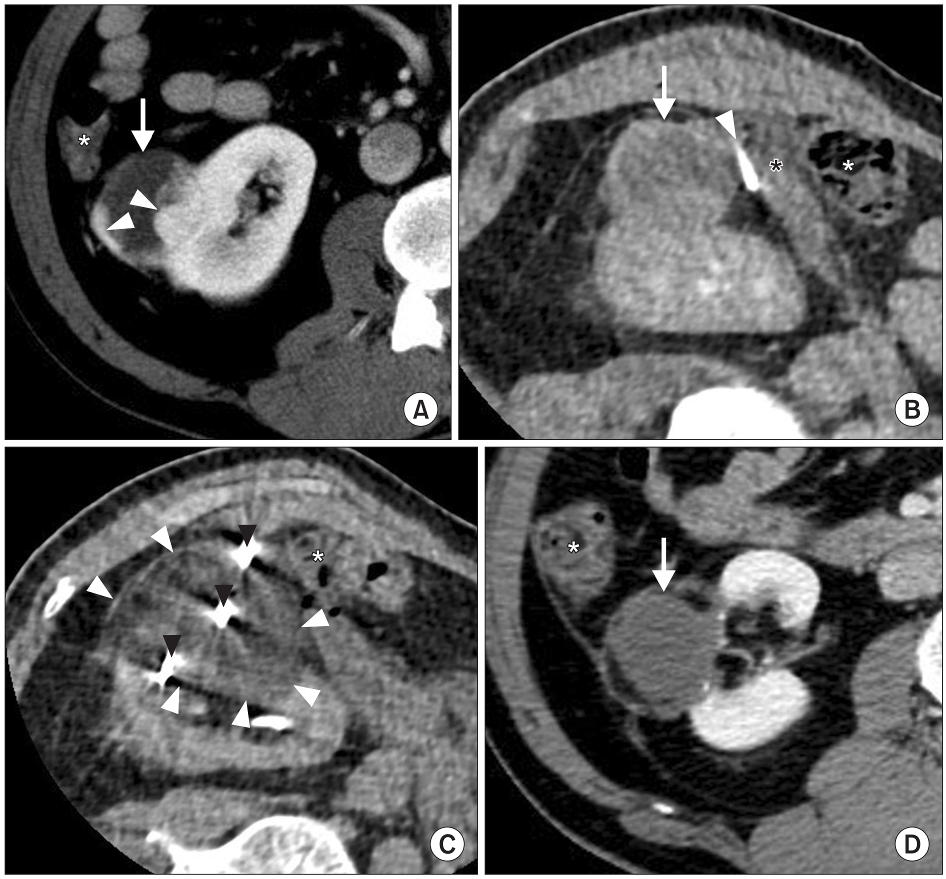

Fig. 1. Computed tomography (CT)-guided cryoablation in a 60-year-old male with a Bosniak IV cyst. (A) Contrast-enhanced axial CT image shows a 4.6 cm right Bosniak IV cyst (white arrow) containing solid components (white arrowheads). The tumor is close to the ascending colon (white asterisk). It was histologically confirmed as clear cell renal cell carcinoma (RCC) with CT-guided biopsy. (B) The patient was lied in the right antero-oblique position to displace ascending colon (white asterisk) from the right RCC (white arrow), but the tumor-to-bowel distance was less than 5 mm. Therefore, hydrodissection was performed with 5% dextrose water (black asterisk), which was injected with an 18-gauge needle (white arrowhead). (C) Axial CT image shows a large ice-ball formation (white arrows) around the multiple cryo-applicators (black arrowheads). It does not cover the ascending colon (white asterisk). (D) Contrast-enhanced axial CT image, which was obtained 30 months following cryoablation, shows no local tumor progression at the right cystic RCC (white arrow). Ascending colon (white asterisk) is unremarkable.

several days.

2. Thermal ablation

1) Types of ablations

The appropriate ablation modality is important for achieving technical success without complications. The size or location of the RCCs may influence the type of ablations selected due to differences in treatment outcomes. Accordingly, cryoablation or MWA can be useful for tumor sizes more than 3 cm given that these techniques can create a larger ablation area than RFA using a single electrode [49,50]. For RCCs located in the renal sinus, however, cryoablation is superior to RFA or MWA owing to less urothelial damage [22,51,52]. For an RCC less than 3 cm and not located in the renal sinus, no differences between ablation modalities in terms of oncologic outcomes or major complications have been noted. As such, RFA still remains a good option for treating small RCC (less than 3 cm) given its generally lower costs compared to cryoablation or MWA.

Economic status and insurance systems are important when selecting an ablation modality. For instance, RFA has been more frequently performed in Korea given its much lower costs compared to cryoablation or MWA. This may be attributed to difference in economic status between Korean and Western individuals. Moreover, the Korean government does not reimburse patients undergoing cryoablation or MWA as much as they do patients undergoing RFA. However, cryoablation has been found to be more common than RFA in Taiwan and Japan considering the sufficient reimbursements provided by their governments.

2) Guiding modalities

The choice of the guiding modality is also important for achieve successful renal tumor ablation. CT remains the most preferred guiding modality during ablation procedures given the familiarity of interventional radiologists with CT-guided procedures [8,9]. Moreover, this imaging modality can clearly determine the cryoablation margin created by the ice ball during the freezing cycle. In contrast, RFA or MWA may have difficulty clearly displaying the ablation margin during the procedures, requiring greater radiologist experience during estimation. However, one considerable issue with CT guidance is the high radiation exposure of the patients [30]. As such, low-dose CT protocols are strongly recommended in Asian patients with relatively lower body mass indices [29]. Interventional oncologists need to know how to reduce the number, range, tube voltage, and tube current of CT scans [29,30].

US can be used to show or monitor the ablation margin given that the ablation area becomes echogenic during RFA or MWA. This imaging modality is useful for treating exophytic RCCs clearly seen in slim Asian patients. However, more frequent local tumor progression had been reported following US-guided ablation given that posterior US shadowing can result from an echogenic ablation area, which makes it difficult to determine whether the tumor margin and the RCC had been completely ablated [3,48]. However, local tumor progression tends to be more frequent following US-guided thermal ablation because posterior US shadowing resulting from echogenic ablation area makes it difficult to determine if the tumor margin as well as the RCC is completely ablated [36]. MRI is not commonly used to for RFA guidance due to its high cost and low availability of MRI-compatible RF electrodes. RFA uses an electrical current, which can disturb the magnetic field. Accordingly, MRI is not useful for RFA guidance considering that image distortion occurs during ablation procedures. Furthermore, MRI-compatible electrodes and devices have yet to be commercially available.

3) Bosniak III or IV cysts

Considering that a higher Bosniak classification has been associated with increased incidence of RCC, surgical intervention is recommended for Bosniak III or IV cysts [53-55]. Reports have shown relatively high diagnosis rates of benign Bosniak III cysts, approximately 50% of which have been confirmed to be RCC postoperatively [56,57]. In contrast, approximately 90% of Bosniak IV cysts have been postoperatively confirmed to be RCC [55]. Although percutaneous biopsy can be performed for these cysts, poor yields have been documented [47] given that the solid component of Bosniak III and IV cysts is much smaller than similar sized solid renal masses. One study showed that the biopsy diagnosis rates for Bosniak III and IV cysts is only approximately 50% [47]. Leakage of cystic fluid may increase the risk of cancer seeding. Park et al. [58,59] reported that RFA promotes higher recurrence-free survival rates in patients with Bosniak III or IV cysts despite most of the cystic masses not having been proven to be RCCs. Cryoablation and MWA can also provide excellent treatment outcomes for these cysts (Fig. 1) [60,61]. Only a few studies have determined the long-term outcomes of thermal ablation treatment for Bosniak III or IV cysts. Considering the modest evidence level, thermal ablation should be selectively performed in patients who cannot undergo surgery.

3. Thermal ablation modalities

1) Radiofrequency ablation

RFA has been known as the first ablation modality for treating RCC. RFA delivers electrical current to the tumor tissue where it induces ionic agitation to increase the temperature over 60℃, leading to cell death [62-65].

The standard RFA protocol includes an initial electrical power of 30–40 W that is increased by 10 W per minute with 2 breaks/roll-offs during ablation [66,67]. Compared to other ablation modalities, RFA is a more well-established technique with more clinical results available for analysis; however, blood flow can limit the size of the ablative zone [68]. Given the hypervascular nature of most RCCs and the kidney, achieving complete ablation is occasionally difficult. Multipolar or multiple-electrode switching systems can be used to reinforce treatment effects [65,69].

In USA, local control rates of T1a RCCs can range from 91% to 100% [11,70-73], and are comparable to those among Asians, which can range from 95% to 100% [70,74,75]. Moreover, estimates have shown that the 5-year overall survival and cancer-specific survival rates among patients with T1 RCC can range from 72% to 97% and 96% to 97% in the USA, respectively [11,67,71,76]. On the other hand, estimates in Asian countries have found that the same survival rates can range from 78% to 90% and 96% to 100%, respectively [70,74,77].

RFA has been found to have complication rates comparable to those of partial nephrectomy, with major complication rates following RFA of T1 RCCs ranging from 0% to 13% [69,70,72,74,76,78,79]. Hemorrhage has been the most frequent complication, which is often self-limiting [67,78,80,81]. Urothelial injuries are quite not common but are more frequent compared to cryoablation, with reported incidence rate ranging from 2% to 10% [67,76,78,82].

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2) Cryoablation

Cryoablation induces cell death through repeated freezing and thawing (Fig. 1). Accordingly, tumor cell injury occurs due to two physiologic events [83], namely osmotic dehydration [84] and intracellular freezing. The predominance of one type of injury mechanism over the other depends on the cooling rate, end temperature, time held at the minimum temperature, and thawing rate [85]. Cryoablation sessions consist of double freeze–thaw cycles involving 10 to 15 minutes of freezing and 8 to 10 minutes of thawing. The double freeze cycle produces significantly larger areas of necrosis than single freezing, regardless of the thaw process [86].

Cryoablation has several advantages over RFA or MWA. First, cryoablation has been associated with more tolerable pain and lesser urothelium damage [22,51,52]. Second, cryoablation promotes fewer incidences of ureter obstruction or urine leakage compared to the other modalities when treating central RCCs. Third, the cryoablation zone is much clearer on MRI and CT. Fourth, applying multiple probes simultaneously allows for greater flexibility in the shape of the isotherm. Fifth, the ability to change the approach trajectory and control the rate at which temperature changes in each individual applicator make cryoablation more feasible compared to other modalities [49].

Studies have shown that cryoablation provides excellent local control rate for T1a RCCs, with reported 5-year recurrence-free survival rates exceeding 90% [28,87,88]. Despite having higher local recurrence rates compared to surgery, cryoablation can be an alternative treatment for T1b RCCs among poor surgical candidates [13,89-91]. Bleeding or hematuria has the most common complication following cryoablation. Moreover, ureter strictures, colon perforations or fistulas, and nerve injuries have been reported, albeit rarely. Evidence has shown that the incidence of major complications is significantly associated with tumor size [14,28,87,92,93].

3) Microwave ablation

Despite having been clinically available for a shorter period of time compared to other modalities, MWA has been found to be apparently safe and effective for the management of renal tumors [94]. MWA, which induces cell death through water molecule agitation, allows for high tissue temperatures and a large ablation area over a short amount of time [95-97]. MWA is not particularly influenced by heat sink effects when treating RCCs around large vessels [95-97]. The kidney is a highly perfused organ with approximately four times the perfusion of the liver [41]. MWA can be performed simultaneously with multiple probes to ablate larger tumors [50].

The standard MWA protocol routinely used for renal tumor ablation includes setting the main frequency to 2,450 MHz, power output to 50 W for 10 minutes [98]. A single antenna can be used to treat smaller RCCs (≤3.0 cm), while and two or more antennas are used for larger ones (>3.0 cm).

A recent meta-analysis reported no difference in local recurrence and cancer-specific mortality between MWA and nephron-sparing surgery [16]. Moreover, the same study found that MWA had relatively low complication rates that were similar to those of other ablation modalities [16]. Nonetheless, further investigations are necessary to determine the long-term safety and oncological outcomes of MWA.

4. Post-ablation considerations

1) Post-ablation imaging follow-up

Appropriate follow-up is also important to determine the presence of local tumor progression. Contrast-enhanced CT or MRI has been considered the best imaging modality for assessing renal function following renal tumor ablation [15,18]. Among patients with chronic kidney disease, unenhanced MRI including diffusion-weighted imaging may be used for post-ablation assessment given the need for contrast material [15,18]. Although contrast-enhanced US can be a good option for follow-up examination, it requires a steep learning curve to obtain sufficient skill.

Unfortunately, no general consensus has been established regarding the follow-up interval. Typically, a 6-month interval is recommended until 2 years post-ablation. Thereafter, annual follow-up is recommended until 5 years post-ablation.

2) Influence on renal function

Several studies found no significant decrease in renal function following thermal ablation for sporadic RCC [28,70,74,87,88]. However, larger tumor sizes, endophytic locations, multiple tumors, and multiple sessions can result in loss of renal function [99]. Nonetheless, such conditions are present when ablating tumors with larger margin [99]. These phenomena frequently occur when treating hereditary RCCs [18,19,25] and T1b RCCs [77]. Granted that renal function was not affected by thermal ablation, patients with hereditary RCCs do not have to rely on dialysis even when all recurrent tumors are treated without local tumor progression. However, thermal ablation lengthens the dialysis-free survival period [18,99] considering that it tends to preserve renal function better compared to surgery.

CONCLUSIONS

Image-guided ablation therapy can be expected to become increasingly popular among Asian countries as the necessity for minimally invasive treatments gains traction as an alternative to partial nephrectomy. Therefore, Asian interventional oncologists need to be familiar with the first version of the ACTA guidelines. For the safe and satisfactory performance of renal tumor ablation in Asian patients with RCCs, they should know pre-ablation and post-ablation considerations.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Byung Kwan Park, Shu-Huei Shen, Masashi Fujimori, and Yi Wang. Data acquisition: Byung Kwan Park. Statistical analysis: Byung Kwan Park. Data analysis and interpretation: Byung Kwan Park, Shu-Huei Shen, Masashi Fujimori, and Yi Wang. Drafting of the manuscript: Byung Kwan Park, Shu-Huei Shen, Masashi Fujimori, and Yi Wang. Critical revision of the manuscript: Byung Kwan Park, Shu-Huei Shen, Masashi Fujimori, and Yi Wang. Administrative, technical, or material support: Byung Kwan Park. Supervision: Byung Kwan Park. Approval of the final manuscript: Byung Kwan Park, Shu-Huei Shen, Masashi Fujimori, and Yi Wang.

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