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Feasibility study of a novel rectal cooling system for hypothermic radical prostatectomy in a swine model

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Thermal damage and inflammatory responses of the sphincter and neurovascular bundles (NVBs) are responsible for post-prostatectomy incontinence and erectile dysfunction. Intraoperative hypothermia in the pelvic cavity may reduce the occurrence of these complications. We evaluated the feasibility of a novel rectal cooling system using an animal model. A novel rectal cooling system consisting of a cooling console and a multi-lumen rectal balloon was developed. We conducted animal tests on male pigs to evaluate the efficacy and safety of the system. The primary endpoint was to maintain the temperature of the NVBs at 25°C (±5°C) during and after the electrocauterization of the bladder neck for 10 seconds. The safety endpoint was device-related complications or significant changes in the core body temperature of the pigs. The NVB temperature was below 30°C within 3 minutes of activation of the rectal balloon. The temperature of the proximal NVB was consistently maintained below 25°C in all cases. The temperature 1 cm from the bladder neck did not rise above 38°C and dropped to the initial level within 1 minute after electrocauterization. During cooling, the minimum temperature at the apex of the prostate was reduced to 10.1°C. There were no device-related complications or significant changes in core body temperature throughout the experiment. Animal tests suggest the feasibility and safety of this novel rectal cooling system. A first-in-human trial to assess the safety and efficacy of this system during radical prostatectomy is warranted.

Keywords: Animals; Erectile dysfunction; Hypothermia; Prostatectomy

INTRODUCTION

Thermal damage and inflammatory responses of the urinary sphincter, bladder neck, and neurovascular bundles (NVBs) contribute to post-prostatectomy incontinence and erectile dysfunction caused by ablation, traction, and the use of thermal energy during surgery [1,2]. Several attempts have been reported to prevent secondary damage from inflammatory reactions and nerve injury by reducing the extent and degree of thermal damage [1,3].

Finley et al. [1,4] reported that secondary inflammation, subsequent cell edema, and apoptosis can be prevented by

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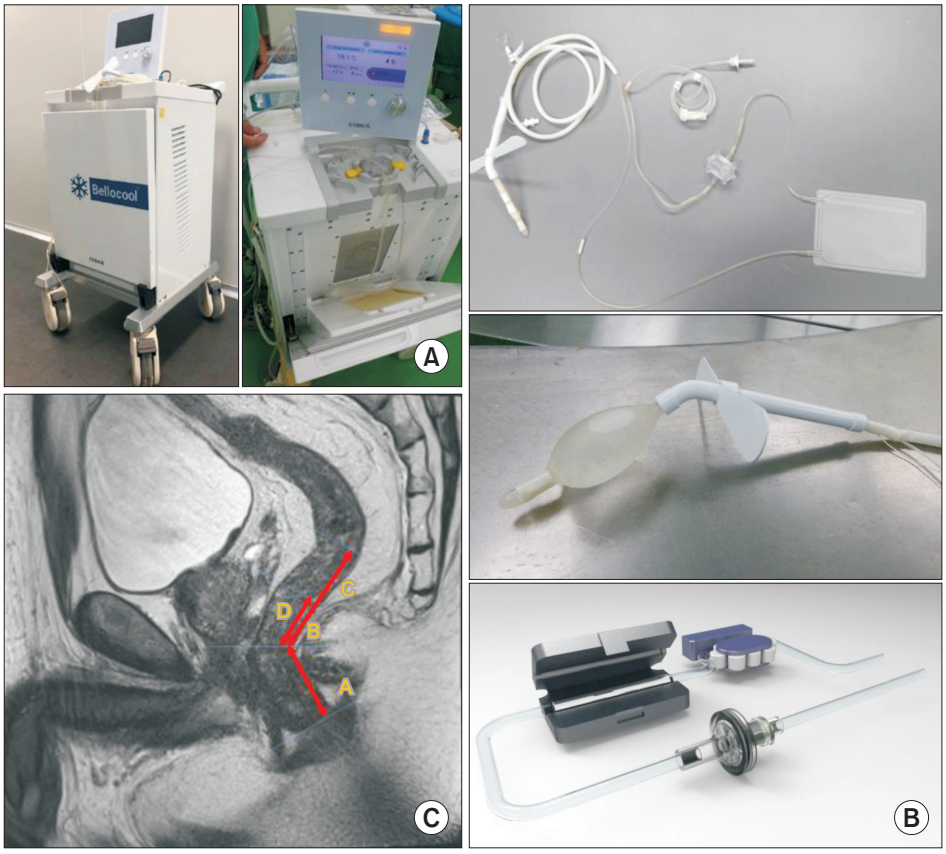

Fig. 1. Novel rectal cooling system. (A) Rectal cooling system. (B) Multi-lumen balloon catheter with bag for cooling water and check valve for pressure control. (C) Preoperative prostate magnetic resonance imaging. A, 32.8 mm; B, 23.1 mm; C, 44.3 mm; D, 60 degrees.

maintaining the pelvic cavity at a low temperature during surgery. Patients whose rectal temperature was lowered using a transrectal cooling balloon during the operation showed a significantly higher rate of continence remission and faster recovery than those in the control group [1,5]. In particular, patients with the lowest rectal temperature achieved 100% postoperative recovery from urinary incontinence [1]. However, a recent randomized controlled trial of regional hypothermia on urinary continence during robot-assisted radical prostatectomy failed to demonstrate its clinical benefit [6], despite several promising retrospective studies [1,4,5].

We developed a novel rectal cooling system, BelloCool™ (CEBIKA, Uiwang, Korea), that has advanced controls and a highly optimized balloon design based on magnetic resonance images of the prostate. The system consists of a cooling console with a control panel and a multi-lumen rectal balloon. The purpose of the rectal cooling system is to induce regional hypothermia in the pelvic cavity, especially around the NVBs, and consequently to minimize thermal spread and secondary inflammation during pelvic surgery, including radical prostatectomy. We conducted a preclinical evaluation to confirm the feasibility and safety of the novel rectal cooling system.

MATERIALS AND METHODS

1. Rectal cooling system

Fig. 1 shows the novel rectal cooling system developed by our group. A multi-lumen catheter was constructed to enable circulation of cooled water (4°C normal saline), temperature and pressure measurement, and additional injection or drainage of circulating water. The catheter had four holes: two holes were used for circulation of the cooled water and two for temperature and pressure measurements. The outer diameter of the catheter was 12 mm, the two holes used to circulate cooling water were designed to be 4.5 mm in diameter, and the two holes used to measure temperature and pressure were designed to be 2.5 mm in diameter. For ease of operation, the tip of the catheter was designed to be inclined at approximately 140° based on an analysis of magnetic resonance images of the prostate. We developed several prototypes of the cooling console and determined the final design, as shown in Fig. 1, after testing the minimum temperature of the cooling plate, time to achieve the target temperature, maximum flow rate of the circulation pump, noise, performance of the check valve, and pressure stability. The goal of the system was to maintain the temperature of the NVBs below 25°C (±5°C) under all conditions.

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2. Preclinical study design

This study was approved by the Institutional Animal Care and Use Committee (approval no. 17-0190-S1A0) of Seoul National University Hospital. A male swine (domestic crossbred pig, approximately 16 weeks old) model was used to mimic human radical prostatectomy. The primary endpoint of efficacy was to maintain the temperature at the proximal NVB around the prostate base at 25℃ (±5℃) or lower during and after electrocautery at the bladder neck. The safety endpoint was a significant change in core body temperature or any device-related complications, including rectal sphincter injury and mucosal injury in the rectum of the pigs.

3. Experiment using animal model

The operating room temperature and core body temperature of the pigs (measured from the esophagus) were monitored throughout the experiment. A blanket warmer was placed underneath the pig and maintained at 38.5℃, which is the basal body temperature of pigs [6].

A total of four male pigs weighing 46.0 to 54.5 kg were used (49.1±3.71 kg). The pigs were fasted for 12 hours the day before surgery. Sedation was induced by the intramuscular administration of tiletamine and zolazepam for injection (Zoletil, Virbac, Seoul, Korea; 5 mg/kg) and xylazine (2 mg/kg). Intubation was performed with the pig in the supine position, and the depth of anesthesia was maintained under 2.0% to 2.5% isoflurane with normoxia (SpO_2 98%) and normocapnia ($EtCO_2$ 38–40 mmHg). An intravenous infusion of normal saline was maintained.

The pelvic cavity was opened using a lower-midline incision. After exposing the bladder, prostate, rectum (including the NVB), and pelvic muscle, a rectal balloon was inserted, and baseline temperatures were measured at each site. We insufflated the balloon with precooled normal saline by activating the cooling console. We measured the temperature at each site until it stabilized.

The temperature was measured at 1 cm above the bladder neck and proximal NVB at the base of the prostate during and after 10 seconds of electrocoagulation of the left and right sides of the bladder neck by setting the monopolar electrocautery to 35 W for up to 80 seconds in 10-second intervals with or without regional hypothermia using the novel rectal cooling system.

Temperature was measured by using a contact-type digital thermometer (SK-1260, SATO, Tokyo, Japan). The tests were repeated thrice, and the average temperatures were determined.

The pigs' core body temperature was monitored throughout the experiments. In the last part of the experiment, we examined the rectal sphincter and mucosa to assess for device-related complications. After the examination, the pigs were euthanized by injection of potassium chloride.

All numerical data are expressed as the mean value and standard error. IBM SPSS (version 23.0, IBM Corp., Armonk, NY, USA) was used for the statistical analyses.

RESULTS

During precooling, the temperature of the normal saline circulating in the cooling system dropped more than 4℃ within 20 minutes. Fig. 2 shows the temperature change in 30-second intervals at each body site after insertion and activation of the precooled rectal balloon. The initial mean temperatures of the rectal balloon, cooling plate, rectum

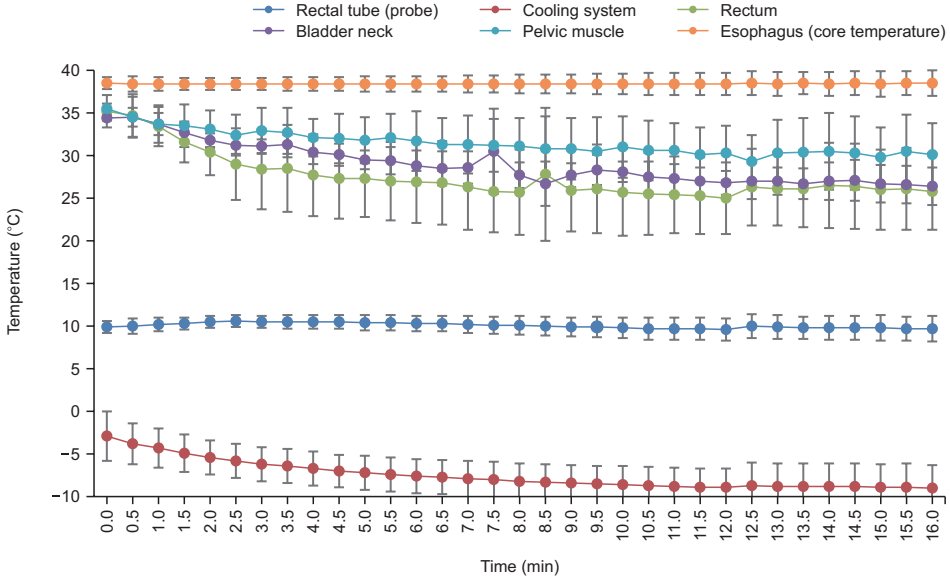

Fig. 2. Temperatures measured at 30-second intervals at each site before electrocauterization with precooled rectal cooling tube.

and NVB, bladder neck, pelvic muscle, and esophagus (core body temperature) were 9.9℃±0.7℃, -2.9℃±2.9℃, 35.2℃±1.9℃, 34.4℃±0.3℃, 35.5℃±0.6℃, and 38.5℃±0.5℃, respectively. Within 2 minutes and 30 seconds, the temperature of the rectum and NVB were reduced to below 30℃ and remained constant at approximately 25℃ after 7 minutes and 30 seconds. The temperature of the bladder neck was maintained below 30℃ after 5 minutes. Core body temperature did not change significantly over time.

Fig. 3 shows a photograph of the experiment in which temperatures during and after electrocoagulation were measured at the bladder neck. Fig. 4 shows the changes in temperature during and after electrocauterization for 10 seconds at each site, without rectal cooling as a control. When the right side of the bladder neck was electrocauterized for 10 seconds, the temperature rose to 41.6℃±0.6℃ and did not fall below 37℃ even after 80 seconds. The temperature of the proximal NVB at the base of the prostate rose to 40.0℃±0.8℃ and did not fall below 37.8℃±0.3℃ even after 80 seconds.

In contrast, the temperature of the NVBs on both sides remained low, approximately 25℃ or lower, even during electrocoagulation (Fig. 5). The temperatures of the left and right sides of the bladder neck increased to 37.2℃±2.7℃ and 37.0℃±1.7℃, respectively. After electrocauterization, the temperature decreased to below 30℃ after 50 and 40 seconds, respectively. During cooling, the minimum temperature of the distal NVB at the apex of the prostate dropped to 10.1℃.

DISCUSSION

The inflammatory response of the bladder and sphincter to ablation and traction is a major cause of incontinence

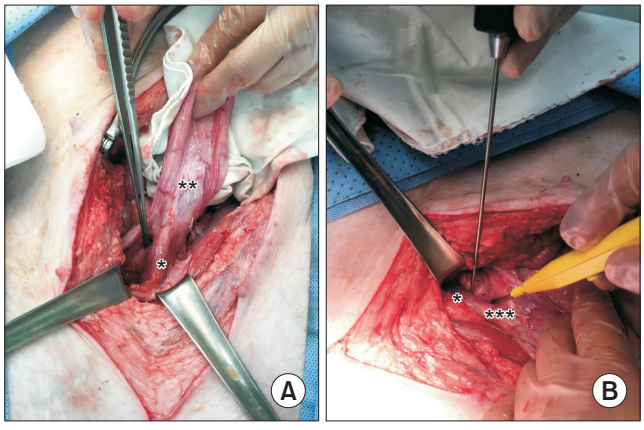

Fig. 3. Operative images. (A) Image of the prostate and bladder exposed. (B) Measurement of temperature by electrocauterization of the right side of the bladder neck. Forceps and temperature probes point to the main neurovascular bundle. *Prostate, **Bladder, ***Bladder neck.

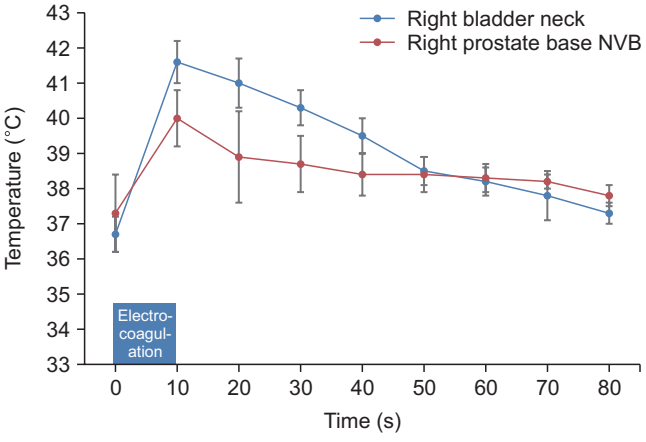

Fig. 4. Changes in temperature before and after electrocauterization (35 W) for 10 seconds at each site without the cooling rectal tube for the control group. NVB, neurovascular bundle.

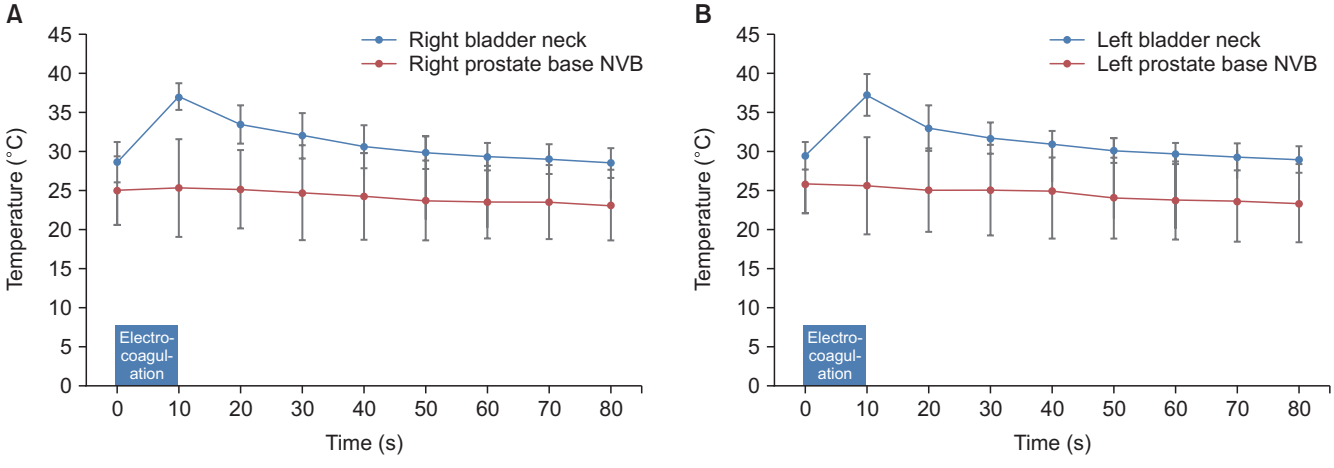

Fig. 5. Changes in temperature before and after electrocauterization (35 W) for 10 seconds at right side (A) and left side (B) with the precooled rectal tube. NVB, neurovascular bundle.

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after radical prostatectomy. Several studies reported that hypothermia in the pelvic cavity can be induced through insertion of a rectal cooling balloon and intracorporeal irrigation of cold water to reduce the inflammatory reaction, and such cooling has been associated with early recovery from incontinence [1,4,5,7,8]. Compared with that in the control group, the incidence of postoperative urinary incontinence was approximately 20% lower in patients who used the rectal cooling balloon (4℃) in the study by Finley et al. [4]. In addition, the continence recovery period was approximately 20 days faster than in the control group. In a follow-up study, patients with a lower rectal temperature during surgery showed a significantly higher rate of continence remission and faster recovery than those in the control group [1,5]. In particular, patients with the lowest rectal temperature achieved 100% postoperative recovery from urinary incontinence [1].

However, a recent multicenter randomized confirmatory trial could not prove the beneficial effect of regional hypothermia on urinary continence during robot-assisted radical prostatectomy using the same device [6]. Thus, we focused on improving device performance for effective cooling. We developed a novel rectal cooling system, BelloCool™, that has advanced controls and a highly optimized balloon design based on prostate magnetic resonance images. The system consists of a cooling console with a control panel and a multi-lumen rectal balloon. The optimized balloon design enhances contact with the NVBs. The system adopts the direct circulation of cooled water rather than indirect cooling and air filtering functions. Air inside the balloon can interfere with the heat exchange between human tissue and cooled normal saline.

The effectiveness of hypothermic treatment can vary for several reasons. Cell death due to thermal damage starts at approximately 45℃, and protein degradation occurs as a result of thermal damage [9,10]. Heat shock proteins play a role in preventing protein degradation due to thermal damage, reversibly correcting the reaction in the temperature range of 0 to 47℃ [11-13]. However, when high heat of 45℃ or more is applied, the damage caused by heat shock proteins results in protein denaturation, agglomeration of proteins, and irreversible protein damage [14,15]. In addition, thermal injury damages the outer membrane of intracellular mitochondria, generating reactive oxygen species and inducing apoptosis and inflammation due to protein destabilization [16].

The development of novel rectal tube cooling systems based on the concept of hypothermia combined with an improved surgical technique may help to improve surgical outcomes. Other research groups compared postoperative outcomes using similar designs of endorectal cooling tubes to maintain hypothermia in the pelvic cavity or around the lesions [5,8,17-21]. Our group quantitatively analyzed anatomical structures in the pelvic cavity using preoperative magnetic resonance imaging (MRI) and applied these data to the design of a multi-lumen balloon catheter. Through repeated laboratory optimization studies, we developed a micro-rectal tube cooling system with a rapid cooling time in which we could precisely control the temperature and pressure and which did not generate noise. To improve the effect of heat radiation and to avoid the use of a fan, the system and heat radiation parts of the cooling modules were connected through a heat pipe. We also developed a pump to circulate cooling water to minimize the driving noise of conventional rotary pumps.

The purpose of this study was to evaluate the safety and feasibility of this rectal tube cooling system using an animal model (male pigs). The time required for the cooler to reduce the temperature by 4℃ is considered an important parameter. In the first animal experiment, it took 30 minutes for the cooler to reach the 4℃ mark, but this time was shortened to 16 minutes in the second animal experiment. If the precooling time is too long, the preparation time before surgery is increased. However, in this experiment, the target temperature of 4℃ was achieved in as little as 16 minutes. Later modifications and adjustments to the length of the rectal cooling tube, use of refrigerant, and the device design significantly reduced the precooling time. When electrocauterization was performed without a cooling rectal tube, the temperatures of the bladder neck area and prostate base NVBs rose to 41.6℃ and 40.0℃, respectively. However, when electrocoagulation was performed, the ambient temperature of tissues did not rise above 37.2℃, and the temperature dropped to the initial level within 1 minute. In particular, the temperature of the bilateral NVB around the prostate base, 1 cm away from the electrocoagulation site, remained constant at 25℃ or less without any change in temperature [22]. The minimum temperature around the apex of the prostate was maintained at 10.1℃. Similarly, in a study analyzing thermal MRI in real time while cooling the pelvic cavity with an endorectal cooling ball, the muscle and perirectal tissue were cooled to 8℃ to 10℃, and the penile stalk and surrounding tissues were cooled to 10℃ to 15℃ [23]. However, we have an excellent system that can maintain the temperature around the apex of the prostate at approximately 10℃ during electrocoagulation. In another similar study, with regional pelvic cooling below 30℃ during robot-assisted radical prostatectomy, pad-free continence after 1 year in the hypothermia group compared with the control group was

96.3% vs. 86.6% (p<0.001), and potency after 15 months was excellent at 83% vs. 66%, respectively [5,18]. Our novel rectal cooling system could reduce thermal damage and inflammatory response by maintaining hypothermia at a much lower temperature of approximately 25℃ around the prostate base NVBs during electrocoagulation, and it may improve continence and erectile function after prostate cancer surgery.

This study has several limitations. First was the small number of animals. However, because this was a feasibility study, we could measure the technical and *in vivo* properties of the device and confirm the safety of the procedure using the minimum number of animals. Second, considering that this was an initial preclinical experiment, all evaluations were performed by open surgery with a midline incision, even though contemporary radical prostatectomy is usually performed by a robot-assisted laparoscopic approach.

CONCLUSIONS

This study demonstrated the safety and feasibility of a novel rectal cooling system through animal testing. The system took a short time of 2 minutes and 30 seconds to precool the rectum to below 30℃ and 7 minutes and 30 seconds to maintain the temperature at 25℃. During electrocauterization with a rectal tube cooling system, the prostate base NVB area was kept constant at 25℃ from the beginning, and the bladder neck area did not rise above 37℃ and immediately fell to the initial level within 30 seconds. This temperature was maintained without a change in the animal's core body temperature throughout the experiment. By applying our novel rectal cooling system with these excellent properties, safe hypothermia can be induced during radical prostatectomy. The rectal cooling system may reduce thermal injury and secondary inflammation in the pelvic cavity, contributing to the maintenance of continence and erectile function and rapid recovery after surgery. Therefore, first-in-human clinical feasibility trials are warranted.

CONFLICTS OF INTEREST

This system was invented by Chang Wook Jeong, Jung Chan Lee, and Hee Chan Kim.

FUNDING

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AUTHOR'S CONTRIBUTIONS

Research conception and design: Jung Chan Lee, Hee Chan Kim, and Chang Wook Jeong. Data acquisition: Won Hoon Song, Inyoung Sun, Gwan Jang, Jeong Hoon Lee, Jae Hyeon Jeong, and Chang Wook Jeong. Statistical analysis: Won Hoon Song. Data analysis and interpretation: Won Hoon Song and Chang Wook Jeong. Drafting of the manuscript: Won Hoon Song and Chang Wook Jeong. Critical revision of the manuscript: all authors. Obtaining funding: Chang Wook Jeong. Administrative, technical, or material support: Jung Chan Lee, Hee Chan Kim, and Chang Wook Jeong. Supervision: Chang Wook Jeong. Approval of the final manuscript: all authors.

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