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Preventive effects of self-administered cryotherapy on paclitaxel-induced peripheral neuropathy in patients with early-stage breast cancer: a propensity score analysis

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We hypothesized that suppression of peripheral circulation *via* cryotherapy may be effective in preventing paclitaxel-induced peripheral neuropathy (PIPN). Therefore, this study aimed to clarify whether self-administered cryotherapy could prevent PIPN in patients with early-stage breast cancer, using real-world data. A single-center, retrospective, observational study was conducted. Data from the electronic medical records of consecutive patients aged ≥ 20 years with early-stage breast cancer who received a regimen containing paclitaxel for 12 cycles with or without self-administered cryotherapy at the National Cancer Center Hospital from March 2018 to May 2019 were evaluated. The primary endpoint was the cumulative dose of paclitaxel until the onset of grade ≥ 2 PIPN. To compare the difference between the two groups, multivariable Cox proportional hazards models adjusted for prognostically important variables were used. Ninety Japanese patients were included in this study. The estimated incidence of grade ≥ 2 PIPN was 26.9% and 37.7% in the self-administered cryotherapy group and control group, respectively (P = 0.314). The multivariable Cox proportional hazards model showed that the self-administered cryotherapy group had a decreased risk of onset of grade ≥ 2 PIPN (hazard ratio: 0.63, 95% confidence interval: 0.25 to 1.39; P = 0.281). Sensitivity analyses using multivariable Cox proportional hazards models along with two propensity score-adjusted methods demonstrated consistent results. The findings suggest that the methods of self-administered cryotherapy may prevent PIPN and should be reinforced appropriately in clinical practice. A randomized controlled multicenter trial of self-administered cryotherapy is warranted.

1. Introduction

In Japan, it is expected that one in two Japanese will develop cancer, and one in three Japanese will die of cancer. Especially among adolescents and young adults, breast cancer has caused serious issues in women (Bray et al. 2018). Anthracycline and taxane are key drugs for treating patients with breast cancer in a neo-adjuvant, adjuvant, or palliative setting (Sparano et al. 2008; Mieog et al. 2007; Seidman et al. 2008). However, chemotherapy-induced peripheral neuropathy (CIPN) induced by taxane and platinum remains an unresolved issue in clinical practice. Paclitaxel-induced peripheral neuropathy (PIPN) results in the most common non-hematological, dose-limiting, adverse reactions, which are observed in 42–70% of patients in such settings, and also reduces the patients' quality of life (QOL) (UpToDate, Paclitaxel (conventional): Drug information, 2020).

According to the American Society of Clinical Oncology guideline, the antidepressant duloxetine is recommended only for the pain management, but not prophylaxis, of CIPN induced by taxane and platinum (Hershman et al. 2014). Furthermore, several clinical studies have reported that the administration of the Japanese herbal medicine Goshajinkigan, the antihyperalgesic drug pregabalin, and vitamin B_{12} had no significant preventive effect on CIPN (Oki et al. 2015; Takenaka et al. 2013; Hirayama et al. 2015). To date, there have been no reports elucidating how to prevent PIPN. Recently, Hanai et al. (2018) conducted a self-controlled trial on cryotherapy with flexible frozen gloves and socks which showed a significant preventive effect on PIPN. Cryotherapy reduces the exposure of the peripheral circulation of paclitaxel. However, the availability of cryotherapy is limited for patient care because many hospitals do not have enough equipment and manpower for cryotherapy. Furthermore, the flexible frozen gloves and socks (Elasto-Gel®, 84400 APT Cedex, Akromed, France) used for cooling peripheral hands and feet and studied by Hanai et al. (2018) were recalled following a litigation against it for frostbite in the United States of America (The United States Food and Drug Administration, 2018). At our hospital, after a press release by Hanai et al. in October 2017 (Kyoto University Research Information Repository, 2018), several patients have undergone self-administered cryotherapy based on cooling goods other than flexible frozen gloves and socks (Hanai et al. 2018). However, their efficacy and safety are unknown because self-administered cryotherapy depends on patient procedures. Based on the findings by Hanai et al. (2018), we hypothesized that suppression of peripheral circulation via cryotherapy may be effective and safe for preventing PIPN even through a variety of cooling goods and methods.

Therefore, the present study aimed to clarify whether self-administered cryotherapy could prevent PIPN in patients with early-stage breast cancer, using real-world data.

2. Investigations and results

2.1. Patient characteristics

A flowchart illustrating the patient enrollment process is shown in Fig. 1. Based on the exclusion criteria, 77 patients were excluded from the analysis. Data from 90 patients were evaluated in this study. The baseline patient characteristics are presented in Table 1. Of these patients, 26 were in the self-administered cryotherapy group and 64 were in the control group. Overall, except for treatment regimens, the baseline patient characteristics were well balanced between both groups. The median age of the patients in the self-administered cryotherapy group and the control group was 51 years (interquartile range: 32–78 years) and 52 years (interquartile range: 29–78 years), respectively.

2.2. Endpoint

The cumulative dose of paclitaxel until the onset of grade ≥ 2 PIPN at the primary endpoint is shown in Fig. 2. The estimated incidence of grade ≥ 2 PIPN was 26.9% and 37.5% in the self-administered cryotherapy and control groups, respectively (P = 0.314). As shown in Table 2, the multivariable Cox proportional hazards model demonstrated that self-administered cryotherapy had a decreased risk of onset of grade ≥ 2 PIPN hazard ratio: [HR]: 0.63, 95%, confidence interval [CI]: 0.25 to 1.39; P = 0.281. Additional multivariable Cox proportional hazards models with two propensity score-adjusted methods showed similar results: inverse probability of treatment weighting (IPTW) method showed a HR: 0.62 with 95% CI: 0.27 to 1.43 (P = 0.264) and another method that

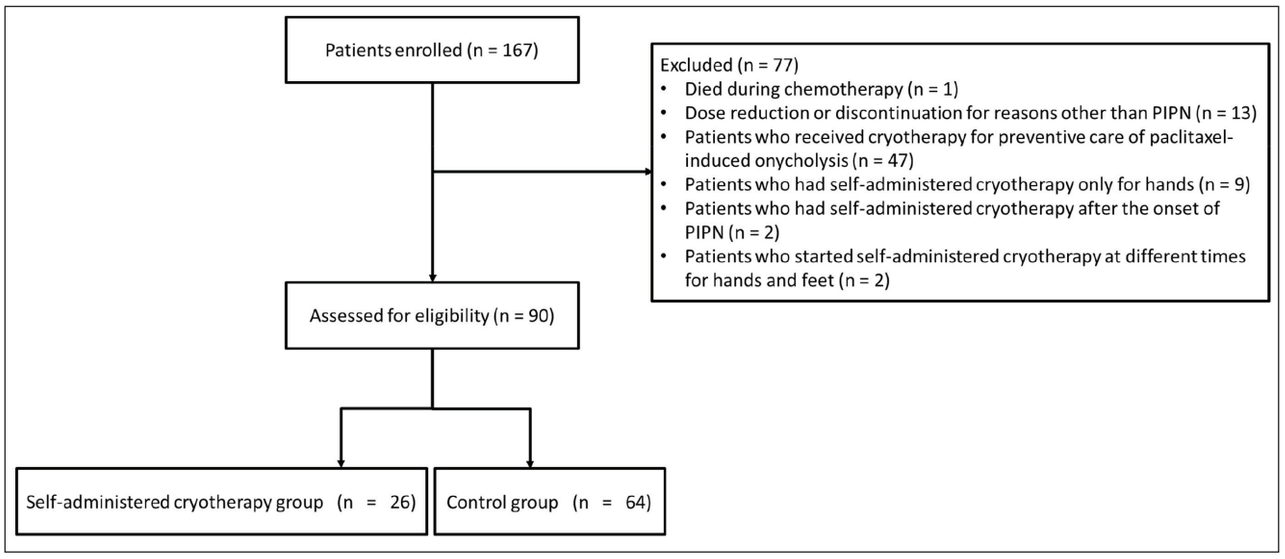

Fig. 1: Patient enrollment flowchart PIPN, paclitaxel-induced peripheral neuropathy

Table 1: Baseline patient characteristics

Characteristic	Self-administered cryotherapy group (n = 26)	Control group (n = 64)
Age, median [interquartile range] (years)	51 [32–78]	52 [29–78]
BMI (kg/m^2)		
BMI < 25	18 (69.2%)	50 (78.1%)
BMI ≥ 25	8 (30.8%)	14 (21.9%)
Treatment setting		
Neo-adjuvant chemotherapy	11 (42.3%)	28 (43.8%)
Adjuvant chemotherapy	15 (57.7%)	36 (56.3%)
Primary site		
Non-bilateral	25 (96.2%)	62 (96.9%)
Bilateral	1 (3.8%)	2 (3.1%)
Regimen		
PTX	19 (73.1%)	37 (57.8%)
PTX + HER ± PER	7 (26.9%)	27 (42.2%)
Prior treatment		
Yes	26 (100%)	61 (95.3%)
No	0 (0%)	3 (4.7%)
Diabetes mellitus		
Yes	1 (3.8%)	2 (3.1%)
No	25 (96.2%)	62 (96.9%)
Concomitant drugs		
Yes	19 (73.1%)	44 (68.9%)
No	7 (26.9%)	20 (31.2%)

BMI, body mass index; PTX, paclitaxel; HER, trastuzumab; PER, pertuzumab.

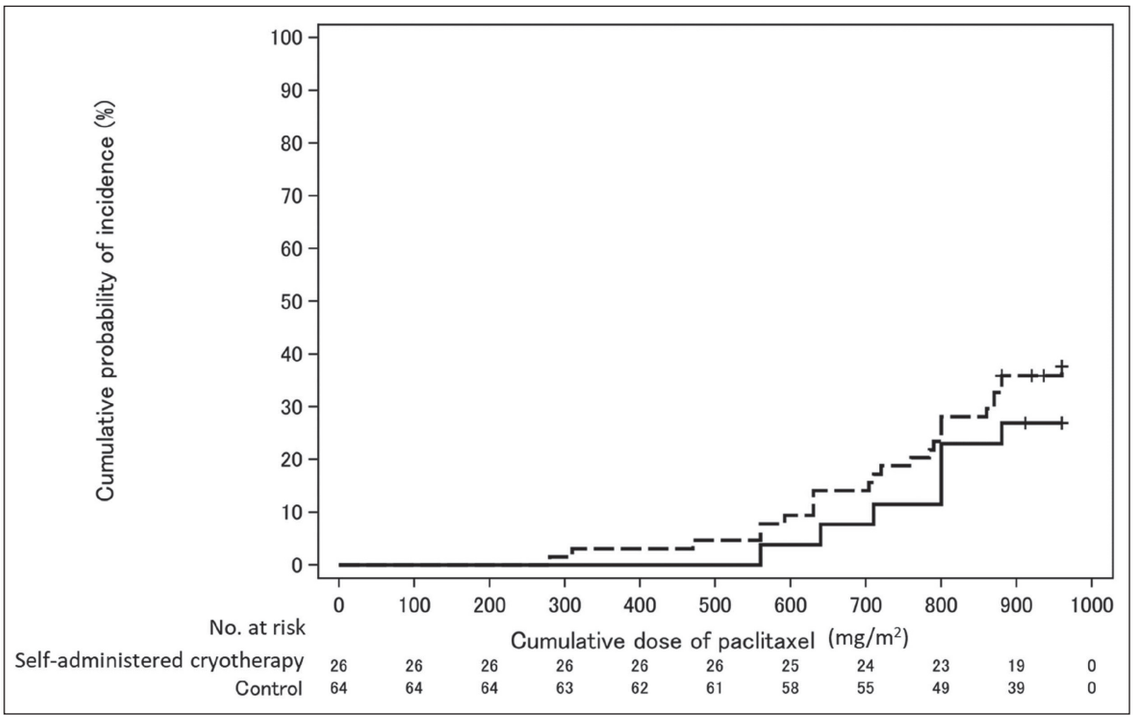

Fig. 2: Kaplan–Meier survival curves for the cumulative dose of paclitaxel until the onset of grade ≥ 2 PIPN The solid line indicates the self-administered cryotherapy group (n = 26), and the dashed line indicates the control group (n = 64).

included the propensity score as an additional covariate showed a HR: 0.63 with 95% CI: 0.27 to 1.48 ($P = 0.290$).

At the secondary endpoint, the proportion of patients with grade ≥ 2 PIPN was 26.9% (n = 7) in the self-administered cryotherapy group compared with 37.5% (n = 24) in the control group (risk difference: –10.6%, 95% CI: –28.6% to 11.4%, $P = 0.339$). The proportion of patients who required any stepwise dose reduction of paclitaxel due to PIPN was 11.5% (n = 3) in the self-administered cryotherapy group, compared with 31.3% (n = 20) in the control group (risk difference: –19.7%, 95% CI: –34.0% to 0.4%, $P = 0.052$). The proportion of patients who required two-step dose reduction of paclitaxel was 7.8% (n = 5) in the control group. In contrast, none of the patients required two-step dose reduction of paclitaxel in the self-administered cryotherapy group. The proportion of patients who discontinued paclitaxel due to PIPN was 0% (n = 0) in the self-administered cryotherapy group, compared with 10.9% (n = 7) in the control group (risk difference: –10.9%, 95% CI: –20.9% to 3.1%, $P = 0.103$). These results showed a higher risk of grade ≥ 2 PIPN in the control group than in the self-administered chemotherapy group. Additionally, there were no cryotherapy-related issues, including litigation for frostbite.

3. Discussion

In the present study, we found that self-administered cryotherapy decreased the risk of onset of grade ≥ 2 PIPN in patients with early-stage breast cancer. To date, there has been limited information on non-pharmacological interventions such as cryotherapy and surgical glove compression therapy for CIPN in a clinical setting. We hypothesized that suppression of peripheral circulation *via* cryotherapy may be effective and safe in preventing PIPN, even with a variety of cooling goods and methods.

Table 2: Multivariable Cox proportional hazard model, IPTW analysis, and propensity score-adjusted analysis of the onset of grade ≥ 2 PIPN

		Multivariable analysis		IPTW		Adjusted for propensity score	
Variables		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Self-administered cryotherapy	Yes	0.63 (0.27–1.46)	0.281	0.62 (0.27–1.43)	0.264	0.63 (0.27–1.48)	0.290
	No	1		1		1	
BMI	≥ 25 kg/m²	1.45 (0.64–3.28)	0.370				
	< 25 kg/m²	1					
Diabetes mellitus	Yes	0.91 (0.11–7.26)	0.926				
	No	1					
Propensity score	(0.1 points)					1.34 (0.61–2.95)	0.465

BMI, body mass index; HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting.
Multivariable Cox proportional hazard model, IPTW analysis, and propensity score-adjusted analysis were used to compare the difference between the two groups. Propensity score model was adjusted for age, BMI, and diabetes mellitus.

Table 3: Paclitaxel regimens

Regimen	Drug and date of administration	Interval	Scheduled course number
wPTX	PTX: 80 mg/m^2, day 1	7 days	12
wPTX + wHER	PTX: 80 mg/m^2, day 1 HER: 4 mg/kg (loading dose) or 2 mg/kg (maintenance dose), day 1	7 days	12
PER + HER + wPTX	PTX: 80 mg/m^2, day 1, 8, and 15 HER: 8 mg/kg (loading dose) or 6 mg/kg (maintenance dose), day 1 PER: 840 mg/body (loading dose) or 420 mg/body (maintenance dose), day 1	21 days	4

wPTX, weekly paclitaxel; wHER, weekly trastuzumab; PER, pertuzumab.

Cryotherapy for preventive PIPN has not been established in patients treated with paclitaxel. Several studies clearly defined the temperature of cooling goods before use, the cooling time, and the timing of changing the goods during cryotherapy (Beijers et al. 2020; Sato et al. 2016; Shigematsu et al. 2020). In previous studies, methods of cryotherapy depended on the researchers. For example, cryotherapy was started at -20 °C 15 min before the start of the infusion and changed every 60 min until 15 min after the end of the infusion. Shigematsu et al. (2020) reported that in patients (n = 22) with breast cancer receiving paclitaxel, the incidence of grade ≥ 2 PIPN was 9.1% in the cryotherapy group. This outcome had great efficacy. In contrast, the present study showed that the incidence of grade ≥ 2 PIPN was 26.9% in the self-administered cryotherapy group. We believe that the differing cooling methods produced this discrepancy. Considering that blood flow was reported to decrease by about 50% when the epidermal temperature fell to about 20 °C (Nillson 1987), maintenance of the temperature may be important for the preventive effect. Importantly, this study showed no cryotherapy-related issues, including litigation for frostbite. Because the patients in this study performed this procedure voluntarily, it is assumed that cooling was discontinued when the temperature became unbearably cold. Consequently, safety was preserved even though the preventive effect of PIPN was insufficient.

In the present study, there was a discrepancy of paclitaxel exposure between the two groups based on clinical practice due to the study design. The proportion of patients who required any stepwise dose reduction of paclitaxel due to PIPN in the self-administered cryotherapy group was less frequent compared with that in the control group (11.5% vs. 31.3%). Additionally, the proportion of patients who discontinued paclitaxel due to PIPN in the self-administered cryotherapy group was much less frequent compared with that in the control group (0% vs. 10.9%). The primary endpoint in the self-administered cryotherapy group was at a disadvantage compared to that in the control group. Therefore, the same conditions of paclitaxel exposure are needed to confirm the findings of our hypothesis. In the present study, the number of patients in the self-administered cryotherapy group was 26. Hence, a pivotal clinical study with sample size calculation is required to confirm the efficacy of self-administered cryotherapy. A sample size of 148 with 96 events is required to have 80% power, assuming that the 3-month incidence rates of grade ≥ 2 PIPN are 25% and 40% in the self-administered cryotherapy and control groups, respectively, and 1-year registration period was assessed at a two-sided significance level of 5%. Therefore, a randomized controlled multicenter trial of the self-administered cryotherapy is needed to confirm our hypothesis. The present study had the following limitations. First, this was a single-center, retrospective, observational study rather than a multi-center, prospective, interventional study. Although we used a multivariable Cox proportional hazard model adjusted for potentially important variables to help account for the non-randomized administration, we were not able to account for unmeasured confounders. Subsequently, we could not collect information about specific cooling methods from the medical records. Taken together, we could not evaluate individual cooling methods; for example, what item was used for cryotherapy, cooling time, and cooling temperature. Second, sample size was relatively small. This study was underpowered to detect the clinical efficacy because we planned this study after the press release by Hanai et al. (2018). Third, long-term toxicity was unknown because it was only evaluated after administering 12 courses of paclitaxel. PIPN often persists after the end of treatment and reduces the patients' QOL. Because the frequency of visits to the hospital after administration of paclitaxel varied, this study could not evaluate coasting effect after the chemotherapy ended. As mentioned earlier, there are currently only few facilities that can perform cryotherapy. It is hoped that more effective and safer methods of cryotherapy will become widely used in the future.

As mentioned above, despite the fact that PIPN significantly lowers patients' QOL and affects the effectiveness of treatment, no effective treatment has been established until now. In addition, PIPN is a subjective side effect that is difficult to assess objectively and may be overlooked. We should once again be deeply aware of these facts as medical professionals. We hope that the only cryotherapy which has been shown to be effective for the prevention of PIPN will be established and promoted for wide-spread use.

To our knowledge, this is the first study to demonstrate that self-administered cryotherapy decreases the risk of onset of grade ≥ 2 PIPN in patients with early-stage breast cancer in a clinical setting. The study findings suggest that the methods of self-administered cryotherapy may prevent PIPN and should be reinforced to improve the patients' QOL, considering the positive results of previous studies. A randomized controlled multicenter trial to confirm the efficacy of self-administered cryotherapy is warranted.

4. Experimental

4.1. Study design

This study had a single-center, retrospective, observational design. It was carried out at the National Cancer Center Hospital, a high-volume cancer center in Tokyo, Japan, using data retrieved from electronic medical records. The methodology of this observational research adhered to the STROBE guidelines (University of Bern 2009) and was in line with those in other related publications by our co-authors (Uchida et al. 2018; Kawazoe et al. 2020, 2018). The study population included consecutive patients aged ≥ 20 years with early-stage breast cancer who received up to 12 cycles of the paclitaxel regimen in neo-adjuvant or adjuvant settings between March 2018 and May 2019.

Patient records were anonymized and analyzed anonymously. The collected data included those on the patients' baseline age; sex; body mass index (BMI); treatment setting; primary site; regimen; prior treatment; diabetes mellitus; cumulative dose and cycle of paclitaxel; concomitant drugs including opioids, non-steroidal anti-inflammatory drugs, antiepileptic drugs, or antidepressants; use of cryotherapy; PIPN; and cryotherapy-related issues including litigation for frostbite.

The exclusion criteria were as follows: 1) death before 12 cycles of paclitaxel, 2) discontinuation of treatment and/or dose reduction before 12 cycles of paclitaxel for reasons other than PIPN; 3) use of flexible frozen gloves and socks for the preventive care of paclitaxel-induced onycholysis; 4) self-administered cryotherapy after the third course of paclitaxel therapy; and 5) lack of patient information.

The study protocol was approved by the ethics committee of the National Cancer Center Hospital (approval number: 2019-302), and the study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research involving Human Subjects mandated by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan. Japanese law does not require individual informed consent to be obtained from participants in non-invasive observational trials, such as the present study. Therefore, we used the official website of the National Cancer Center Hospital as an opt-out method rather than acquiring written or verbal informed consent from each patient.

4.2. Paclitaxel regimen

All patients received paclitaxel weekly in combination with premedications such as dexamethasone 6.6 mg (8 mg as dexamethasone sodium phosphate), ranitidine

50 mg, and DL-chlorpheniramine 10 mg over 30 min of intravenous infusion before paclitaxel in accordance with the package insert. Paclitaxel was diluted with 250 mL of 5% glucose solution and administered at 80 mg/m^2 over one hour of intravenous infusion every week with or without administering trastuzumab ± pertuzumab (Table 3). The dose of paclitaxel and the treatment schedule were modified at the clinicians' discretion according to the toxicity profiles.

4.3. Self-administered cryotherapy

In the present study, the self-administered cryotherapy group included the patients who underwent cryotherapy applied to both hands and feet, as mentioned earlier, in the first or second courses of paclitaxel therapy. In contrast, the control group included patients who did not undergo cryotherapy. In the self-administered cryotherapy, the patients voluntarily conducted cryotherapy on their own, using various cooling goods and methods including ice packs, refrigerants, cold 500 mL bottle-covered towels, and ice gloves. Flexible frozen gloves and socks were not used. Additionally, the patients changed the cooling goods as needed during paclitaxel infusion.

4.4. Endpoint

The primary endpoint was the cumulative dose of paclitaxel until the onset of severe PIPN at any point during or after the administration of paclitaxel. If a patient did not experience this event, the cumulative dose of paclitaxel was detected at the date of the last treatment of paclitaxel. Severe PIPN was defined as grade ≥ 2, according to the Common Terminology Criteria for Adverse Events, version 4.0 (National Cancer Institute 2010). The secondary endpoint was the proportion of patients who decreased or discontinued paclitaxel treatment due to PIPN. In addition, cryotherapy-related issues including litigation for frostbite were also evaluated. The above-mentioned assessment was repeated during paclitaxel treatment or at the last administration of paclitaxel by physicians, pharmacists, and nurses at each patient visit.

4.5. Statistical analysis

Kaplan-Meier curve analysis and log-rank test were used to compare the difference between the self-administered cryotherapy and control groups according to the primary endpoint. Subsequently, a multivariable Cox proportional hazards model was used to compare the difference between the two groups. Potential explanatory variables concerning the patients' backgrounds including BMI (≥ 25 vs. < 25 kg/m^2) and diabetes mellitus (yes vs. no) reported in several previous studies were included as independent variables in the multivariable model (Rowinsky et al. 1993; Bao et al. 2016). Additionally, to assess the robustness of results, the difference between the two groups was compared using multivariable Cox proportional hazards models through two propensity score-adjusted methods: the IPTW method and another that included the propensity score as an additional covariate (Austin 2016; D'Agostino 1998). The propensity score of the self-administered cryotherapy group was estimated for each patient using a logistic regression model which included age, BMI, and diabetes mellitus (Rosenbaum and Rubin 1983). HRs and 95% CIs were provided. Categorical data were estimated with 95% CIs calculated using the Newcombe method (Newcombe 1998) and compared using chi-square test or Fisher's exact test, as appropriate. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). According to the recommendation of the American Statistical Association (Wasserstein and Lazar 2016; Wasserstein et al. 2019), strict thresholds should be avoided when interpreting *P*-values. Hence, describing $P < 0.05$ as being statistically significant was avoided. Instead, we interpreted the results on the basis of point estimates with their CIs.

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Contributions of authors Statement: Yumiko Shimanuki and Hironobu Hashimoto contributed to the study concept and design of the clinical study. Hironobu Hashimoto contributed to the data collection. Hitoshi Kawazoe and Ryuji Uozumi performed all statistical analyses. All authors contributed to the interpretation of the results. Yumiko Shimanuki and Hitoshi Kawazoe wrote the initial draft of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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