Erectile dysfunction (ED) is a major complication after radical prostatectomy (RP); however, debate continues regarding the efficacy of penile rehabilitation in the recovery of the postoperative erectile function (EF). This study included a total of 103 consecutive sexually active Japanese men with localized prostate cancer undergoing nerve-sparing RP, and analyzed the postoperative EF, focusing on the significance of penile rehabilitation. In this series, 24 and 79 patients underwent bilateral and unilateral nerve-sparing RPs, respectively, and 10 or 20 mg of vardenafil was administered to 35 patients at least once weekly, who agreed to undergo penile rehabilitation. Twelve months after RP, 48 (46.6%) of the 103 patients were judged to have recovered EF sufficient for sexual intercourse without any assistance. The proportion of patients who recovered EF in those undergoing penile rehabilitation (60.0%) was significantly greater than that in those without penile rehabilitation (38.2%). Of several parameters examined, the preoperative International Index of Erectile Function-5 (IIEF-5) score and nerve-sparing procedure were significantly associated with the postoperative EF recovery rates in patients with and without management by penile rehabilitation, respectively. Furthermore, univariate analysis identified the preoperative IIEF-5 score, nerve-sparing procedure and penile rehabilitation as significant predictors of EF recovery, among which the preoperative IIEF-5 score and nerve-sparing procedure appeared to be independently associated with EF recovery. Considering these findings, despite the lack of independent significance, penile rehabilitation with low-dose vardenafil could exert a beneficial effect on EF recovery in Japanese men following nerve-sparing RP.

Impact of penile rehabilitation with low-dose vardenafil on recovery of erectile function in Japanese men following nerve-sparing radical prostatectomy

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Erectile dysfunction (ED) is a major complication after radical prostatectomy (RP); however, debate continues regarding the efficacy of penile rehabilitation in the recovery of the postoperative erectile function (EF). This study included a total of 103 consecutive sexually active Japanese men with localized prostate cancer undergoing nerve-sparing RP, and analyzed the postoperative EF, focusing on the significance of penile rehabilitation. In this series, 24 and 79 patients underwent bilateral and unilateral nerve-sparing RPs, respectively, and 10 or 20 mg of vardenafil was administered to 35 patients at least once weekly, who agreed to undergo penile rehabilitation. Twelve months after RP, 48 (46.6%) of the 103 patients were judged to have recovered EF sufficient for sexual intercourse without any assistance. The proportion of patients who recovered EF in those undergoing penile rehabilitation (60.0%) was significantly greater than that in those without penile rehabilitation (38.2%). Of several parameters examined, the preoperative International Index of Erectile Function-5 (IIEF-5) score and nerve-sparing procedure were significantly associated with the postoperative EF recovery rates in patients with and without management by penile rehabilitation, respectively. Furthermore, univariate analysis identified the preoperative IIEF-5 score, nerve-sparing procedure and penile rehabilitation as significant predictors of EF recovery, among which the preoperative IIEF-5 score and nerve-sparing procedure appeared to be independently associated with EF recovery. Considering these findings, despite the lack of independent significance, penile rehabilitation with low-dose vardenafil could exert a beneficial effect on EF recovery in Japanese men following nerve-sparing RP.

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RP have been reported; however, the largest trial, conducted in 2008, failed to show the superiority of the daily use of PDE5I as penile rehabilitation over on-demand treatment with PDE5I in the recovery of EF after RP. Therefore, debate continues concerning the significance of postoperative penile rehabilitation, particularly that in Japanese men who are characterized by sexual profiles different from Western populations. Considering these findings, we retrospectively analyzed the features of ED in a total of 103 consecutive Japanese men who underwent nerve-sparing RP, focusing on the significance of penile rehabilitation using low-dose vardenafil in the recovery of postoperative EF.

MATERIALS AND METHODS

Patients
At our institution, RP was performed for 451 Japanese patients with clinically localized prostate cancer between January 2009 and March 2011. After excluding patients treated with androgen deprivation and/or radiotherapy from these 451, this study included a total of 103 consecutive patients who were judged to be sexually active with preoperative International Erectile Function-5 (IIEF-5) score ≥8 and subsequently underwent either bilateral or unilateral RP. Informed consent for performing the present study was obtained from all patients, and the study design was approved by the Research Ethics Committee of our institution. In this series, the procedures for RP and the nerve-spring technique generally followed the methods described by Walsh et al. and the criteria to consider a nerve-sparing procedure were prostate-specific antigen ≤10 ng ml⁻¹, clinically organ-confined tumor and Gleason sum <7.

Evaluation
Preoperative data, including the age at surgery, body mass index, comorbidities (diabetes mellitus, hypertension, hyperlipidemia and cardiovascular disease), serum prostate-specific antigen value and IIEF-5 score, were obtained from all patients. All pathological examinations of resected RP specimens were performed under the guidance of a single pathologist according to the 2002 Tumor, Node and Metastasis classification system. Of the included patients who agreed to receive penile rehabilitation, 10 or 20 mg of vardenafil was administered according to the degree of cardiovascular comorbidities as well as the wishes of the patient at least once weekly within 1 month after RP for 12 months; whereas, the remaining patients did not receive any PDE5Is even as on-demand treatment. Medication compliance of vardenafil was confirmed, when the patients visited the outpatient clinic every 3 months. Twelve months after RP, it was assessed in all patients whether the recovery of EF, defined as the ability to have an erection sufficient for sexual intercourse without any assistance, could be achieved.

Statistical analysis
All statistical analyses were performed using Statview 5.0 software (Abacus Concepts Inc, Berkley, CA, USA). Differences in several parameters according to the postoperative recovery of EF were compared using the chi-square test. Forward stepwise logistic regression analysis was used to determine the association between several parameters and postoperative EF recovery. A value of P < 0.05 was considered significant.

RESULTS
The characteristics of the 103 Japanese patients included in this study are summarized in Table 1. Of the 103 patients, 24 (23.3%) and 79 (76.7%) underwent bilateral and unilateral RPs, respectively, and 35 (34.0%) agreed to undergo penile rehabilitation. Of these 35 patients, 30 and 5 took 10 and 20 mg of vardenafil, respectively, at least once weekly for 12 months, and there was no patient who withdrew from this study because of the side effects associated with vardenafil. There were significant differences in the comorbidities (P = 0.023) and pathological stage (P = 0.011) between patients with and without penile rehabilitation; however, no significant differences were observed in the remaining characteristics examined in this study between these two groups.

Twelve months after RP, 47 (45.6%) of the 103 patients were judged to have recovered EF sufficient for sexual intercourse without any assistance, consisting of 21 with penile rehabilitation and 26 without penile rehabilitation. Therefore, the proportion of patients who recovered EF in those undergoing penile rehabilitation (60.0%) was significantly greater than that in those without penile rehabilitation (38.2%) (P = 0.036). However, there was no significant difference in the IIEF-5 score 12 months after RP between 35 patients with penile rehabilitation (11.1 ± 7.4) and 68 without penile rehabilitation (9.3 ± 7.7). Table 2 shows the impact of several parameters on EF recovery 12 months after RP. Of several parameters examined, the preoperative IIEF-5 score (P < 0.001; <17 vs ≥17) and nerve-sparing procedure (P = 0.0046; bilateral vs unilateral) were significantly correlated with the postoperative EF recovery rate. When patients were divided into two groups according to management with/without penile rehabilitation, the preoperative IIEF-5 score had a significant effect on the postoperative EF recovery in patients undergoing penile rehabilitation (P < 0.001), while the nerve-sparing procedure was significantly associated with the recovery of EF after RP in patients without penile rehabilitation (P = 0.011).

We then conducted univariate and multivariate analysis in order to identify factors predicting the preservation of EF following RP. As shown in Table 3, univariate analysis showed that the preoperative IIEF-5 score (P < 0.001), nerve-sparing procedure (P = 0.038) and penile rehabilitation (P = 0.047) were significantly correlated with the postoperative EF recovery. Furthermore, of these three significant factors, the preoperative IIEF-5 score (P = 0.0013) and nerve-sparing procedure (P = 0.028), but not penile rehabilitation, were identified as independent predictive factors of the recovery of EF after RP.

DISCUSSION
RP is the most widely accepted therapeutic option for the treatment of patients with localized prostate cancer; however, it has been well recognized that ED, which adversely influences the postoperative quality of life, frequently occurs in patients undergoing RP even with the nerve-spring technique. In recent years, the concept of penile rehabilitation was introduced based on the idea that early sexual stimulation and augmented blood flow to the penile tissue would facilitate the return of natural EF as well as the resumption of medically unassisted sexual activity. Although the mainstay of the current penile rehabilitation strategy is the administration of PDE5I, which has been shown to enhance nocturnal erections and oxygenation of the cavernosal tissues, there has not been a standard approach with respect to the use of PDE5I as penile rehabilitation, particularly in Japanese men whose sexual profile is different from that of Western populations. In this study, therefore, we retrospectively reviewed data from a total of 103 consecutive Japanese men who underwent nerve-sparing RP and evaluated the clinical significance of penile rehabilitation with the use of low-dose vardenafil in the recovery of postoperative EF.

In this series, 46.6% of patients were regarded as having EF sufficient for sexual intercourse without any assistance, and the EF recovery rate in patients with penile rehabilitation was significantly
higher than that in those without penile rehabilitation. To date, there have been several clinical studies investigating the efficacy of penile rehabilitation using PDE5I; however, the outcomes have not been consistent. For example, Montorsi et al showed no benefit of daily vardenafil on EF recovery compared with its on-demand use in a randomized trial including 628 patients who were treated with bilateral nerve-sparing RP; however, Briganti et al reported no difference in terms of EF recovery between patients receiving on-demand versus daily PDE5I following bilateral nerve-sparing RP. Such conflicting findings regarding the efficacy of penile rehabilitation with PDE5I could be explained mainly by differences in preoperative parameters, such as the age, EF and comorbidity profile, among these studies; therefore, it is currently recognized that the effectiveness of penile rehabilitation remains ‘unknown’ in humans.

In this series, the preoperative IIEF-5 score was significantly associated with postoperative EF recovery in patients undergoing penile rehabilitation, while the nerve-sparing procedure significantly affected EF recovery in patients who did not receive penile rehabilitation. These findings suggest that it is difficult to expect the sufficient recovery of EF in patients with a lower preoperative IIEF-5 score even after treatment with penile rehabilitation, and that, if bilateral nerve-sparing RP is performed, the recovery of postoperative EF might be favorable irrespective of management by penile rehabilitation. In fact, it had no significant effects on the recovery rate of EF in patients with a lower preoperative IIEF-5 score whether they received penile rehabilitation or not, and there was no significant difference in EF recovery rates between patients with and without penile rehabilitation following bilateral nerve-sparing RP.

It is potentially useful to identify factors that can be used to predict the recovery of EF following RP. In this series, postoperative EF recovery was significantly associated with the preoperative IIEF-5 score, nerve-sparing procedure and penile rehabilitation, of which the IIEF-5 score and nerve-sparing procedure were identified as independent predictive factors in EF recovery. This outcome is supported by several previous studies. For example, Marien et al analyzed the data from 293 patients treated with bilateral nerve-sparing RP, while Gallina et al analyzed the data from 634 patients undergoing RP, while Gallina et al reported that the age, adult-onset diabetes mellitus and nerve-sparing procedure were independently related to the preservation of postoperative potency in 634 patients undergoing RP, while Gallina et al analyzed the data from 293 patients treated with bilateral nerve-sparing RP, and concluded that younger patients with a good preoperative EF may experience a favorable EF recovery. Considering these findings, it may be possible

### Table 1: Patient characteristics

|                     | Overall (n=103) | Penile rehabilitation |
|---------------------|----------------|-----------------------|
|                     | Yes (n=35) | No (n=68) | P  |
| **Age at surgery* (year)** | 63.4±9.2 | 61.8±13.2 | 64.2±12.8 | 0.37 |
| **Body mass index at surgery** (kg m⁻²) | 23.9±5.1 | 22.9±5.9 | 24.4±7.4 | 0.30 |
| **Preoperative IIEF-5 score** | 17.7±4.4 | 18.2±5.6 | 17.4±5.9 | 0.51 |
| **Preoperative serum PSA level** (ng ml⁻¹) | 8.8±6.3 | 8.6±7.6 | 8.9±7.3 | 0.83 |
| **Number of comorbidities (%)** | 0 | 68 (66.0) | 18 (51.4) | 50 (73.5) | 0.023 |
|                     | 1 | 19 (18.5) | 7 (20.0) | 12 (17.7) |  |
|                     | ≥2 | 16 (15.5) | 10 (28.6) | 6 (8.8) |  |
| **Nerve-sparing procedure (%)** | Bilateral | 24 (23.3) | 11 (31.4) | 13 (19.1) | 0.16 |
|                     | Unilateral | 79 (76.7) | 24 (68.6) | 55 (80.9) |  |
| **Pathological stage (%)** | pT2 | 81 (78.6) | 32 (91.4) | 47 (69.1) | 0.011 |
|                     | pT3 | 22 (21.4) | 3 (8.6) | 21 (30.9) |  |

*IIEF: international index of erectile function; PSA: prostate-specific antigen; s.d.: standard deviation. *Values are expressed as mean±s.d.

### Table 2: Recovery of postoperative erectile function according to management with penile rehabilitation

|                     | Overall (n=103) | Penile rehabilitation |
|---------------------|----------------|-----------------------|
|                     | Yes (n=35) | No (n=68) | P  |
| **Age at surgery% (year)** | ≥63 | 23/54 (42.6) | 0.52 |
|                     | <63 | 24/49 (49.0) |  |
| **Body mass index at surgery% (kg m⁻²) (kg m⁻²)** | ≥23 | 26/58 (44.8) | 0.85 |
|                     | <23 | 21/45 (46.7) |  |
| **Preoperative IIEF-5 score (%)** | ≥17 | 36/59 (61.0) | <0.001 |
|                     | <17 | 11/44 (25.0) |  |
| **Preoperative PSA level** (ng ml⁻¹) (%) | ≥9 | 16/40 (40.0) | 0.36 |
|                     | <9 | 31/63 (49.2) |  |
| **No. of comorbidities (%)** | 0 or 1 | 37/87 (42.5) | 0.14 |
|                     | ≥2 | 10/16 (62.5) |  |
| **Nerve-sparing procedure (%)** | Bilateral | 17/24 (70.8) | 0.0046 |
|                     | Unilateral | 30/79 (38.0) |  |
| **Pathological stage (%)** | pT2 | 36/79 (45.6) | 0.98 |
|                     | pT3 | 11/24 (45.8) | 0.001 |

*IIEF: international index of erectile function; PSA: prostate-specific antigen
Penile rehabilitation after nerve-sparing radical prostatectomy
Y Nakano et al

In conclusion, this retrospective study included a total of 103 consecutive Japanese men who were judged to be sexually active and subsequently underwent nerve-sparing RP of whom 35 (34.0%) received penile rehabilitation with low-dose vardenafil. The postoperative recovery rate of EF in men with penile rehabilitation was significantly greater than that in those without penile rehabilitation. Furthermore, despite the lack of independent significance on multivariate analysis, penile rehabilitation appeared to be significantly associated with the sufficient recovery of EF for sexual intercourse. Collectively, these findings suggest that penile rehabilitation using low-dose vardenafil may help preserve the postoperative EF in Japanese men following nerve-sparing RP.

AUTHOR CONTRIBUTION
YN designed the study, analyzed the data and wrote the paper. HM supervised the project and wrote the paper. KC analyzed the data and performed the statistical study. MF supervised the project.

COMPETING INTEREST
The authors have no competing interests.

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