学位論文　博士（医学）甲

Cine magnetic resonance imaging provides novel predictors of early continence recovery after radical prostatectomy: Assessment of the dynamics of pelvic floor muscles.

(Cine MRI を用いた骨盤底筋の動的評価によって得られた前立腺全摘除後の早期尿禁制獲得を予測する新たな指標**)**

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ORIGINAL CLINICAL ARTICLE

Cine magnetic resonance imaging provides novel predictors of early continence recovery after radical prostatectomy: Assessment of the dynamics of pelvic floor muscles

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Abstract

Aims: Postprostatectomy incontinence is a major complication of prostatectomy. Although pelvic floor muscle training can successfully treat postprostatectomy incontinence, evidence for how muscle movement affects continence recovery is lacking. We evaluated dynamic factors of prostatectomy patients using cine magnetic resonance imaging to identify risk factors for postprostatectomy incontinence and reveal the contribution of pelvic floor muscles to continence recovery.

Methods: A total of 128 prostate cancer patients who underwent robot-assisted laparoscopic surgery were enrolled. Cine magnetic resonance imaging was performed preoperatively and 6 months after surgery. Continence was defined as pad-free or use of safety pads. We defined the bladder neck elevation distance during pelvic floor muscle training as the bladder elevation distance. Patients with continence recovery within 1 month comprised the continence group ($n = 48$); other patients comprised the incontinence group ($n = 80$).

Results: The preoperative bladder elevation distance was significantly longer in the continence group than in the incontinence group (10.4 vs. 8.2 mm; $p < .001$). The postoperative bladder elevation distance of the continence group tended to be longer (9.9 vs. 8.9 mm; $p = .057$). Multivariate analysis showed that the preoperative bladder elevation distance significantly contributed to continence recovery ($p = .016$). Patients with a longer preoperative bladder elevation distance (>8.5 mm) experienced continence recovery significantly faster than patients with a shorter distance (<8.5mm) ($p = .038$).

Abbreviations: BED, bladder elevation distance; MRI, magnetic resonance imaging; MUL, membranous urethral length; PFMT, pelvic floor muscle training; PPI, postprostatectomy incontinence; PUVA, posterior urethrovesical angle; RARP, robot-assisted radical laparoscopic prostatectomy; RP, radical prostatectomy; SUI, stress urinary incontinence; tLA, thickness of the levator ani; VBDD, voiding bladder declination distance.

Conclusions: Bladder elevation distance, a novel dynamic parameter, was strongly associated with early continence recovery. Cine magnetic resonance imaging can assess a patient's risk of postprostatectomy incontinence and guide pelvic floor muscle training.

KEYWORDS
bladder elevation, cine MRI, dynamic MRI, incontinence, pelvic floor muscle training, postprostatectomy

1 | INTRODUCTION

Radical prostatectomy (RP) is an effective treatment for localized prostate cancer.[1] However, complications such as urinary incontinence and erectile dysfunction, can lower a patient's quality of life (QOL).[2] Robot-assisted radical laparoscopic prostatectomy (RARP) might allow earlier recovery of continence than open or laparoscopic prostatectomy.[3] However, postprostatectomy incontinence (PPI) remains a concern.

PPI comprises stress urinary incontinence (SUI) and urgency urinary incontinence. Pathogenesis of PPI is thought to be caused by anatomical or functional damage to the urethral sphincter muscle and dominant nerve.[4] Preoperative factors such as age, obesity, and prostate size are predictors for the possibility and degree of PPI.[4] The membranous urethral length (MUL), measured by magnetic resonance imaging (MRI) preoperatively and postoperatively, is associated with PPI.[5–7] Thus, the high accuracy and reproducibility of MRI is a useful tool for predicting PPI.

Preoperative pelvic floor muscle training (PFMT) can improve early continence rates; however, its efficacy is controversial.[8] Using ultrasonography to provide proper instructions for PFMT decreases the PPI rate, and obtaining dynamic real-time information about pelvic floor muscle movement improves guidance.[9,10] In the literature, the bladder elevation was suggested to be a significant indicator of the PFMT efficiency, but there was no statistical analysis for the association between bladder elevation and continence.[10] According to the evaluation using postoperative cystography, the bladder elevation can also be a useful predictor for early continence recovery.[11] However, ultrasonography and cystography are not sufficiently accurate to evaluate PMFT performance and predict early continence recovery.

Cine MRI (real-time MRI) provides dynamic information as consecutive images with high accuracy, is noninvasive, does not involve radiation exposure, and has high reproducibility.[12] It is suitable for monitoring the pelvic viscera motion and has been used to evaluate female SUI and pelvic floor prolapse.[12,13] Unfortunately, there is little data regarding cine MRI usage for evaluating male SUI and PFMT.[14,15]

We hypothesized that the bladder elevation during PFMT would indicate the efficacy of PFMT, and effective PFMT would lead to early continence recovery. To evaluate the bladder elevation, cine MRI is appropriate because of the high accuracy and dynamic information. Therefore, we used cine MRI in patients with prostatectomy to determine if the bladder elevation could be a predictor of early continence recovery, which would thereby implicate the function of the pelvic floor muscles in this process.

2 | MATERIALS AND METHODS

2.1 | Patients

This study enrolled 128 male prostate cancer patients that had undergone prostatectomy at our institution. Surgery was performed during January 2018 and December 2018. This study was approved by the ethical board for epidemiological studies at our institution. All patients provided written informed consent. The exclusion criteria were the existence of apparent dementia, a severe neurological disorder, and chronic renal failure requiring dialysis therapy. All prostatectomy patients in 2018 were 135, and one patient was excluded due to anuria. Two patients refused to participate, and four patients dropped out because of the cumbersome procedure. There was no patient with prior radiation therapy, but five patients had histories of transurethral surgery for benign prostate hypertrophy.

2.2 | Study schedule

Cine MRI was performed preoperatively and at 6 months after surgery. Each patient completed 3 days of 24-h pad tests to assess urinary incontinence. To evaluate the continence status during the first postoperative year, a completed International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) was collected from patients preoperatively, at hospital discharge, and 1, 3, 6, and 12 months after surgery (Figure S1).

2.3 | Definition of continence

Continence was defined as pad-free or the use of safety pads and was confirmed by a 0 ml urinary incontinence volume during the 24-h pad test and a score of 0 on the second completed ICIQ-SF questionnaire. The definition of continence varies with studies,[4–7,16] and there is no common view. We set a slightly strict definition in the present study to avert ambiguity.

2.4 | Surgical procedure

All prostatectomy procedures were performed using robot-assisted laparoscopy and the transperitoneal approach with the da Vinci S(i) surgical robot (Intuitive Surgical, Inc.). Surgery was performed by five trained urologists, and the main surgical process was performed in a similar manner. A nerve-sparing technique was adopted based on the judgment of each surgeon.

2.5 | Cine MRI procedure

Cine MRI was performed using a 1.5-tesla Vintage Titan system (Canon Medical Systems Corporation). Patients were placed in the Fowler position with a full bladder, which is ideal for natural voiding. After multiplanar T2-weighted axial section imaging, an adequate sagittal section was created to capture the prostatic urethra. Three phases were observed with the T2-weighted sagittal section: resting phase, PFMT phase, and voiding phase (repetition time/echo time, 4.2/2.1 ms; flip angle, 60°; slice thickness, 7 mm; interslice gap, 0 mm; field of view, 28 cm; matrix, 192 × 208; time/slice, 0.6 s/1 slice). During scanning, a trained nurse provided patients with guidance in the same examination room. During the resting phase, the patient stayed relaxed without voiding. During the PFMT phase, biofeedback was obtained using cine MRI, and some PFMT trials were observed. The best performance series was adopted for the data analysis. Urine was collected during the voiding phase.

2.6 | MRI measurements

Some dynamic and static parameters were measured by one urologist to standardize the measurement procedure. To improve measurement uncertainty, the urologist received measuring advice from a specialist radiologist. During the resting phase, MUL and thickness of the levator ani (tLA) were measured (Figure 1A-C). During preoperative MRI, the MUL was defined as the distance from the prostatic apex to the upper part of the urethra at the penile bulb; during postoperative MRI, the MUL was defined as the distance from the bladder neck to the upper part of the urethra at the penile bulb.[17] The tLA was defined as the maximal length of the levator ani muscle at the caudal urethra to the prostate apex in the axial section.[16] During the PFMT phase, we used the bladder elevation distance (BED) as a novel parameter. We predicted that BED would indicate PFMT performance, according to the previous studies using ultrasonography and cystography.[10,11] The BED was defined as the maximal distance of bladder neck elevation during PFMT (Figure 1D,E). During the voiding phase, the bladder neck usually relaxes with dilatation of the urethral sphincter. Therefore, we defined a new parameter for the maximal distance of bladder neck declination, which was defined as the voiding bladder declination distance (VBDD; Figure 1F). The posterior urethrovesical angle (PUVA) was measured during the resting phase and voiding phases (Figures 1G,H). The bladder neck descent and the PUVA are considered risk factors for SUI in males and females, indicating urethral hypermobility and intrinsic sphincteric deficiency.[18,19]

2.7 | Statistical analysis

Patients that recovered continence within 1 month comprised the continence group ($n = 48$); and the other patients comprised the incontinence group ($n = 80$; Table 1). We set the division of continence within 1 month because recent studies regarding PPI tend to focus on factors and surgical technique which make continence recovery earlier.[7,17] We analyzed the parameters of the two groups using the Mann–Whitney U test or χ^2 test. We also analyzed the preoperative and postoperative parameters using the Wilcoxon signed-rank test. Preoperative parameters were also analyzed using Cox proportional hazards models to reveal hazard ratios (HRs) and 95% confidence intervals (CIs). For multivariate analysis, we selected BED, MUL, and tLA as the MRI parameters, because these preoperative parameters had tendencies of difference in the two groups analysis ($p < .10$). Moreover, several factors likely to be related to

FIGURE 1 Magnetic resonance imaging measurements. Magnetic resonance imaging parameters were measured in T2-weighted images. (A) Black line indicates the preoperative membranous urethral length (MUL) in the sagittal section. (B) Black line indicates the postoperative MUL in the sagittal section. (C) White line indicates preoperative thickness of the levator ani (tLA) in the axial section. (D) White arrow length indicates the preoperative bladder elevation distance (BED) in the sagittal section. (E) White arrow length indicates the postoperative BED in the sagittal section. (F) Black arrow length indicates the postoperative voiding bladder declination distance (VBDD) in the sagittal section. (G) White angle indicates the postoperative posterior urethrovesical angle (PUVA) in the sagittal section during the resting phase. (H) White angle indicates the postoperative PUVA in the sagittal section during the voiding phase

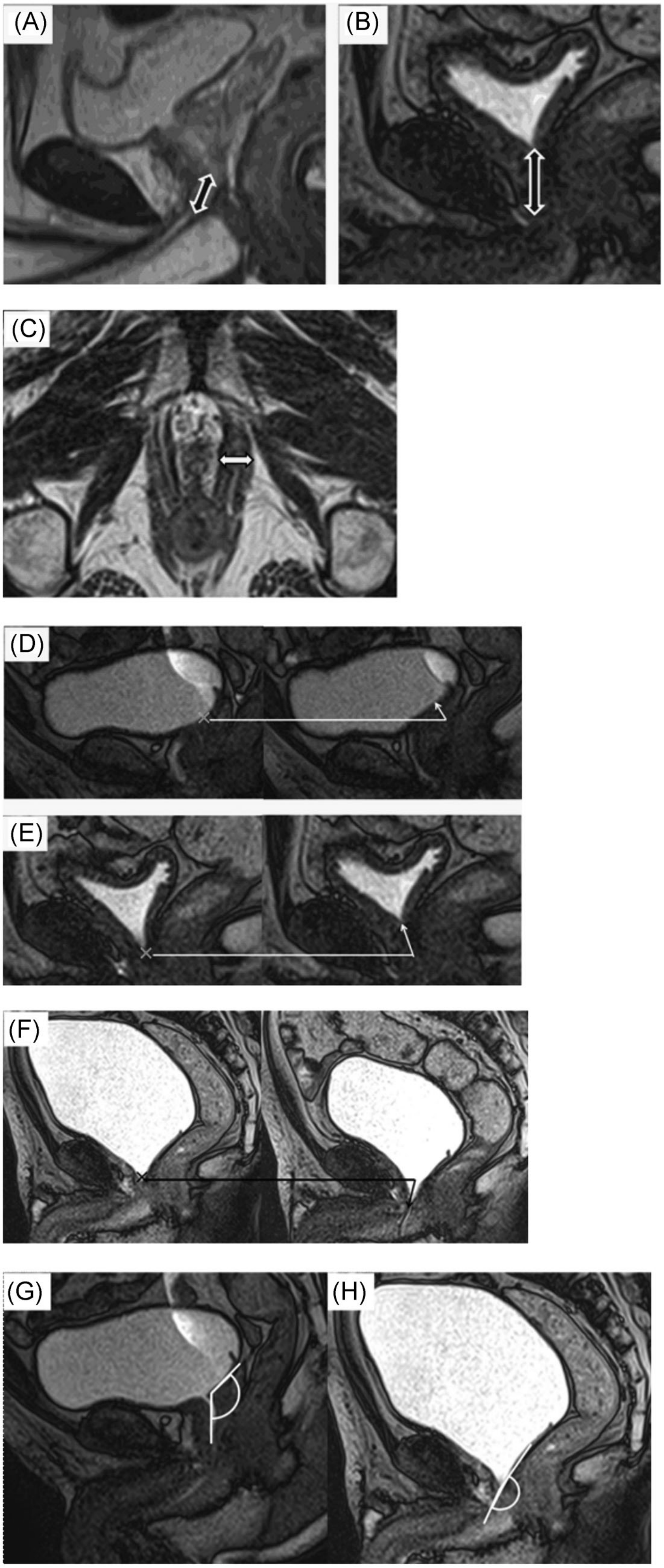

TABLE 1 Patient characteristics

		Continence group ($n = 48$)		Incontinence group ($n = 80$)		
		Median	**Interquartile range**	**Median**	**Interquartile range**	***p***
Age (years)		68	62.8, 73	69	64, 72.3	.986
BMI (kg/m^2)		23.5	21.8, 26.3	24.5	22.5, 25.3	.781
Initial PSA (ng/ml)		6.88	5.46, 12	6.85	5.2, 10	.366
Prostate volume (ml)		35	30, 45	35.5	28.8, 41.3	.609
Operative time (min)		143	124, 174	138	128, 173	.694
Console time (min)		114	93, 140	107	92, 139	.986
Blood loss (ml)		90	70, 173	100	60, 178	.826
		n	%	*n*	%	*p*
pT stage	2	43	89.6	65	81.3	.209
	3	5	10.4	14	17.5	
Gleason score	6	2	4.2	5	6.3	Not applicable
	7	36	75	52	65	
	8	4	8.3	9	11.3	
	9	6	12.5	14	17.5	
Nerve-sparing	No	12	25	24	30	(No/yes) .543
	Unilateral	21	43.8	39	48.8	
	Bilateral	15	31.3	17	21.3	
Lymph node dissection	No	30	62.5	55	68.8	(No/yes) .469
	Unilateral	11	22.9	16	20	
	Bilateral	7	14.6	9	11.3	
Middle lobe		9	18.8	12	15	.5792
Adjuvant ADT		7	14.6	16	20	.4397
History	Hypertension	22	45.8	36	45	.9269
	Hyperlipidemia	9	18.8	17	21.3	.7336
	Diabetes mellitus	6	12.5	14	17.5	.4507
	BPH	6	12.5	12	15	.6937

Abbreviations: ADT, androgen deprivation therapy; BMI, body mass index; BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen.

PPI were also selected: age,[20] prostate-specific antigen (PSA), prostate volume,[3] and nerve-sparing.[21] A Kaplan–Meier analysis with log-rank testing was also performed for the preoperative BED and MUL. The Kaplan–Meier analysis compared the time to continence after RARP between the two groups and divided the results according to the median preoperative BED and MUL values. Statistical analyses were performed using IBM SPSS version 22.0 (IBM Corporation). Significance was considered .05 for all comparisons.

3 | RESULTS

Patient characteristics, perioperative parameters, pathological results, and MRI parameters of the 128 patients are shown in Tables S1 and S2. The median preoperative BED and MUL were 8.55 and 11.00 mm, respectively; these were used for the Kaplan–Meier analysis. Urinary continence rates gradually increased; 93.8% of patients (120/128) achieved continence recovery (Figure S2). There was no significant difference in the patient characteristics, perioperative data, or pathological results with or without the nerve-sparing technique.

Preoperative and postoperative MRI parameters of the continence and incontinence groups were compared (Table 2). The preoperative BED in the continence group was longer than that in the incontinence group (10.4 vs. 8.2 mm; $p < .001$). The postoperative BED of the continence group also tended to be longer (9.9 vs. 8.9 mm; $p = .057$). Only in the postoperative state was the PUVA of the continence group significantly smaller than that in the incontinence group during the resting phase (130° vs. 135°; $p = .005$) and voiding phase (138° vs. 143°; $p = .026$). The postoperative MUL of the continence group was significantly longer (14.5 vs. 12.4 mm; $p < .001$).

The BED became significantly shorter postoperatively in the continence group (10.4 vs. 9.9 mm; $p = .004$). The MUL became significantly longer in the continence group (11.6 vs. 14.5 mm; $p < .001$). After surgery, the PUVA became larger in both the continence and incontinence groups during both the resting and voiding phases ($p \leq .001$).

TABLE 3 Cox proportional hazard model for continence recovery

	HR	95% CI	p
Age (years)	0.9528	0.7803–1.1009	.553
PSA (ng/ml)	1.1036	1.0159–1.1834	.022*
Prostate volume (ml)	1.0464	0.9820–1.1067	.154
Nerve-sparing (yes = 1)	0.8790	0.5510–1.2970	.086
Preoperative BED (mm)	0.9588	0.9242–0.9923	.016*
Preoperative MUL (mm)	0.9560	0.9139–0.9965	.033*
Preoperative tLA (mm)	1.0019	0.9141–1.0344	.412

Abbreviations: BED, bladder elevation distance; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; MUL, membranous urethral length; tLA, thickness of the levator ani.

*$p < .05$.

The multivariate analysis was performed after adjusting for some covariates (Table 3). Cox proportional hazards models showed that the preoperative BED (HR = 0.9588; $p = .016$) and preoperative MUL (HR = 0.9560; $p = .033$)

TABLE 2 Comparison of MRI parameters

	Continence group (n = 48)		Incontinence group (n = 80)		
	Median	Interquartile range	Median	Interquartile range	p
Pre-BED (mm)	10.4	7.8, 14.1	8.2	6.3, 9.9	<.001*
Post-BED (mm)	9.9	7.3, 12.4	8.0	6.0, 10.2	.057
p	.004*		.846		
Pre-VBDD (mm)	9.3	6.6, 10.9	9.3	7.5, 12.2	.320
Post-VBDD (mm)	8.6	6.5, 12.8	8.2	6.3, 11.4	.300
p	.469		.449		
Pre-PUVA (°); resting phase	96	93, 103	95	90, 103	.163
Post-PUVA (°); resting phase	130	123, 135	135	129, 141	.005*
p		<.001*		<.001*	
Pre-PUVA (°); voiding phase	112	105, 115	111	105, 117	.921
Post-PUVA (°); voiding phase	138	128, 144	143	136, 150	.026*
p	0.001*		<.001*		
Pre-MUL (mm)	11.6	10.1, 12.5	10.7	8.9, 12.6	.066
Post-MUL (mm)	14.5	13.2, 17.3	12.4	10.2, 14.2	<.001*
p	<.001*		.084		
Pre-tLA (mm)	10.3	9.2, 11.4	9.5	9.1, 10.7	.084
Post-tLA (mm)	9.6	8.4, 11.2	9.6	8.3, 10.7	.519
p	.081		.339		

Abbreviations: BED, bladder elevation distance; MRI, magnetic resonance imaging; MUL: membranous urethral length; pre-, preoperative, post-, postoperative; PUVA, posterior urethrovesical angle; tLA, thickness of the levator ani; VBDD, voiding bladder declination distance.

*$p < .05$.

significantly contributed to continence recovery. Higher PSA levels resulted in significantly later continence recovery (HR = 1.1036; p = .022).

Kaplan–Meier analysis with log-rank testing (Figure 2A) revealed that patients with a greater preoperative BED (>8.5 mm) experienced faster continence recovery (median time to continence, 1.0 vs. 3.0 months; p = .038). The preoperative MUL was not significantly different in continence recovery time by Kaplan–Meier analysis (median time to continence, 3.0 vs. 3.0 months; p = .220; Figure 2B).

4 | DISCUSSION

This study demonstrates that cine MRI is useful for predicting the PPI risk. Preoperative BED during PFMT, as measured by cine MRI, was strongly associated with early continence recovery. This is the first study to show that cine MRI is useful for digitizing the skill level used during PFMT and predicting the risk of PPI.

The comparison of the two groups showed that a significantly longer preoperative BED in the continence group, which indicated that the patient performed better PFMT, resulting in earlier continence recovery. The tendency for the thicker preoperative tLA in the continence group supports the potential for good PFMT. However, because the postoperative tLA was equal between the two groups, good PFMT was attributed to technical advice regarding how to use the muscles rather than the amount of muscle used. Previous research has also shown that the tLA is not associated with continence recovery.[22] We suppose that PFMT performance is based on muscle strength, neurological factors, and the patient's skill, and that the BED is the result of these multiple factors; therefore, the BED can be evaluated to determine accurate PFMT. In other words, BED could

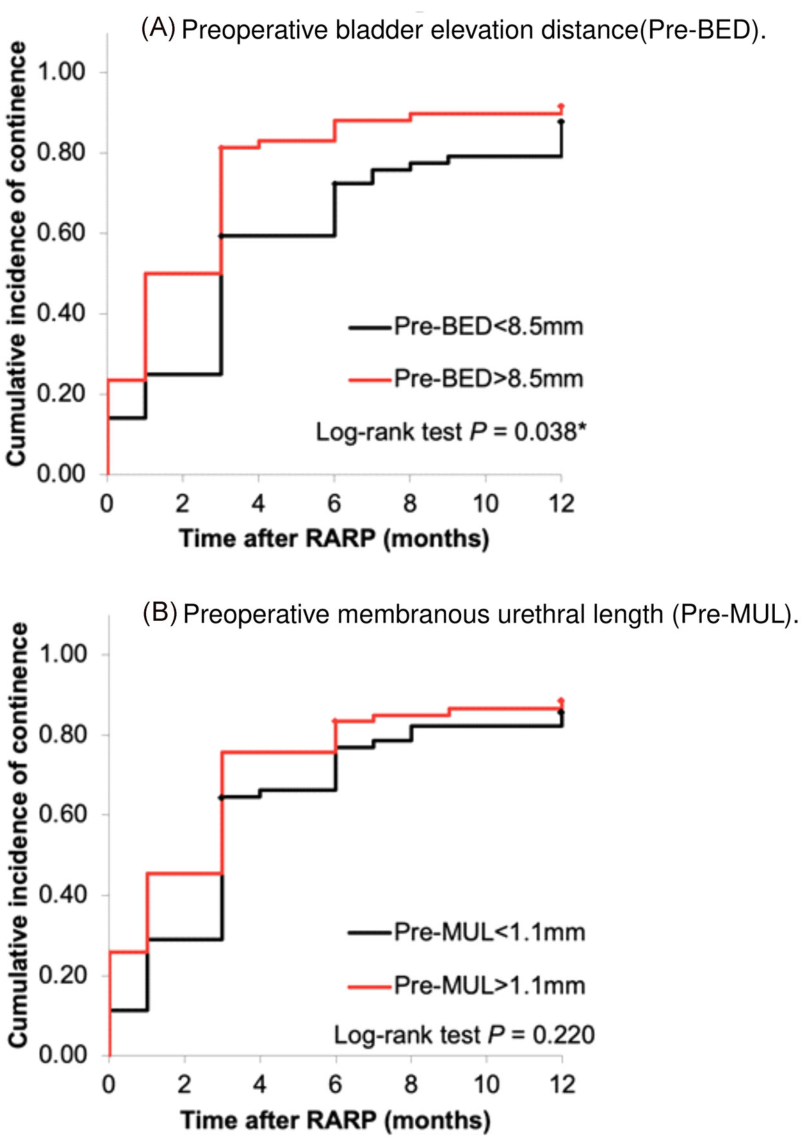

FIGURE 2 Cumulative incidence of continence. Cumulative continence rates after robot-assisted radical laparoscopic prostatectomy (RARP) were compared between two groups divided according to the median values of the preoperative magnetic resonance imaging (MRI) measurements. (A) Preoperative bladder elevation distance. (B) Preoperative membranous urethral length. *p < .05

express the practical function of the muscle, whereas static MRI parameters only express anatomical features of the muscle. The theoretical concept of PFMT is that repeated contraction of pelvic floor muscles may improve strength and efficiency, and close the urethra through enhancing the rhabdosphincter function or the supportive system such as levator ani.[8] We believe that greater BED represents higher urethral closure pressure due to better periurethral muscle function.

It is controversial whether PFMT is effective for PPI because of the difficulty in determining whether correct PFMT was performed. To ensure effective PFMT, several biofeedback techniques are available, such as digital palpation, electromyography, and ultrasonography.[9,23,24] The results of the present study indicate that cine MRI could be adapted for PFMT biofeedback to evaluate the BED. Cine MRI for prostatectomy patients would be useful not only as a predictor of PPI, but also as a biofeedback tool to achieve earlier continence recovery.

The VBDD was not significantly different between the two groups preoperatively and postoperatively, suggesting that urethral hypermobility during voiding is not involved in PPI. Some studies have advocated that a smaller PUVA after RP contributes to early continence recovery.[19,25] In our study, the PUVA of the continence group was significantly smaller than that of the incontinence group during the resting and voiding phases only after surgery, thus supporting the results of previous studies. At our institution, we try to leave the urethra as long as possible and suspend the bladder and urethra to reduce the extent of the PUVA. Such a procedure might affect the extended MUL after surgery, especially in the continence group of the present study; however, according to another study, the MUL usually becomes shorter.[8] These results suggest that the surgical techniques to keep the MUL longer may be effective for promoting earlier continence recovery. Cine MRI could simultaneously measure PUVA and MUL, which predict PPI risk after surgery. Cine MRI, presenting consecutive and three-dimensional images, enables simultaneous multifactor measurements with dynamic and highly accurate data.

MUL has previously been shown to be the most remarkable predictor of early continence recovery after RP.[5,6] In this study, the preoperative BED was a more reliable predictor of continence recovery; showing significant differences in every analysis. Therefore, the BED, which implicates the actual function, maybe more meaningful than the MUL, which only represents anatomy. The usefulness of dynamic evaluation has been previously shown through the evaluation of bladder neck elevation using postoperative cystography.[11] However, preoperative data were not shown in this study, and the measurements captured with only frontal cystography have spatial problems. Cine MRI can provide more accurate data than cystography without preoperative catheterization and radiation exposure. Information obtained with cine MRI can estimate the PPI risk for prostate cancer patients, assist with treatment selection, and help evaluate the need for nerve-sparing.

This study has limitations. First, we did not examine the usefulness of cine MRI to obtain PFMT biofeedback. Cine MRI biofeedback was obtained during only a few trials, and we adopted the data even if the training was not effective. There is also a problem of learning bias. A prospective cohort of two PFMT biofeedback groups with or without cine MRI should be performed. Second, we did not have data regarding abdominal pressure, which may provide clues to the pathogenesis of PPI, as there was insufficient time to conduct another phase. Despite bladder neck hypermobility under abdominal pressure on dynamic MRI not showing significant results in a previous report,[15] it will be important to examine situations involving the use of the pelvic floor muscles under abdominal pressure in future studies. Third, the use of five surgeons might have affected the results. However, using only one surgeon would have resulted in too few patients to be evaluated, and the surgical procedure was standardized. Finally, as this was a single-institution study with a relatively small number of patients, our results need to be verified by multicenter prospective studies. Larger number of patients would also enable analysis for severe incontinence persisting after 1 year, though our results were of significance only in early continence recovery. Further studies of cine MRI for prostate cancer patients might establish new predictors and develop PFMT biofeedback for early continence recovery and improved QOL.

5 | CONCLUSIONS

Our study demonstrates that cine MRI can be used to evaluate the BED as a novel predictor of early continence recovery after RARP. Dynamic and highly accurate data are obtained by cine MRI. Thus, cine MRI can evaluate the PPI risk and has a potential for PFMT biofeedback to help guide early continence recovery.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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