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ORIGINAL ARTICLE

Longitudinal analysis of trifecta outcome in Japanese patients with prostate cancer following robot-assisted laparoscopic radical prostatectomy

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Abstract

Purpose To analyze the trifecta outcome (continence, potency, and cancer control) longitudinally using robot-assisted laparoscopic radical prostatectomy (RARP).

Method We prospectively obtained 1-year longitudinal Expanded Prostate Cancer Index Composite (EPIC) data (preoperative and at 3, 6, 9, and 12 months after RARP) from 291 patients who underwent RARP by a single surgeon. Continence was defined as the use of 'zero or one pads'. Potency was defined as the ability to achieve and maintain satisfactory erections firm enough for sexual activity or sexual intercourse. Continence and potency were subjectively determined from patient-reported outcomes (EPIC question nos. 5 and 18). The biochemical recurrence (BCR) rate was defined as two consecutive PSA levels of > 0.2 ng/mL after RARP. Outcomes of the pentafecta were complications and positive surgical margins combined with the trifecta outcomes.

Results Trifecta was achieved in 4.6, 5.6, 8.1, and 9.6% of all patients at 3, 6, 9, and 12 months, respectively. Pentafecta rates were 2.3, 3.0, 5.1, and 6.1%, respectively. Trifecta rates in the nerve-sparing (NS) group were 12.5, 12.7, 18.9, and 23.6%, respectively. The BCR-free rates maintained a high level and were 94.4, 93.9, 93.9, and 90.9%, respectively. Continence rates were improved to 55.2, 75.5, 81.6, and 85.0%, while the potency rate was extremely low at 7.5, 7.8, 9.8, and 10.9%. Even in the NS group, potency rates remained low at 18.1, 18.6, 21.9, and 26.1%, respectively.

Conclusion This longitudinal analysis of trifecta outcomes may be beneficial and should be used when counseling patients with clinically localized PCa.

Keywords Robot-assisted laparoscopic radical prostatectomy · Sexual function · Quality of life · Trifecta · Longitudinal evaluation

Introduction

With the widespread use of the prostate-specific antigen (PSA) test, patients are now frequently diagnosed with low grade and low-stage prostate cancer (PCa) [1, 2]. Radical prostatectomy (RP) is recognized as an effective treatment for clinically localized PCa. As a result, disease-free survival (DFS) rates approach 90% at 5 years after RP [3]. Other approaches, such as radiation therapy offer a similar DFS. Treatments with comparable DFS rates should be evaluated in terms of quality of life (QOL), including continence and potency [4].

The implementation of the robotic surgical system in the field of urology has brought with it the advantages of three-dimensional binocular magnification, motion scaling, tremor filtration, and favorable surgeon ergonomics, and it has raised new hopes for a minimally invasive approach to RP [5]. Robotic surgery enables more precise operation and a better surgical field, so it was expected that functional recovery can be achieved with widespread use of the robot-assisted laparoscopic radical prostatectomy (RARP) procedure.

Patients' interest tends to rest on maintaining their continence and potency postoperatively, as the prognosis of patients with localized PCa has generally been good. The

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concept of trifecta consists of continence, potency, and cancer control. This trifecta is emphasized as the true endpoint when it comes to patients in the real world. The trifecta consists of different concepts related to cancer recurrence and functional recovery, such as urinary and sexual function. In previous studies, various trifecta rates ranging from 20 to 83% have been reported, and the evaluation points have also varied, ranging from 12 to 54 months [6]. It can extremely difficult to evaluate postoperative outcomes because the cancer recurrence and functional recovery change over time.

This is the first study to analyze longitudinally the trifecta rate in RARP. Our aim is to analyze the trifecta outcome (continence, potency, and cancer control) longitudinally in patients who have undergone RARP.

Patients and methods

We prospectively obtained 1-year longitudinal Expanded Prostate Cancer Index Composite (EPIC) data (preoperative and at 3, 6, 9, and 12 months after RARP) from 458 patients who underwent RARP performed by a single surgeon between May 2010 and April 2018. This questionnaire, together with a stamped return envelope, was mailed to all patients receiving RARP. The number of cases who had incontinence and erectile dysfunction (ED) before RARP were 9 and 160, so we excluded these 167 patients who had incontinence and/or ED at preoperative. Continence was defined as the use of 'zero or one pads'. Potency was defined as the ability to achieve and maintain satisfactory erections firm enough for sexual activity or sexual intercourse. Continence and potency were subjectively determined from patient-reported outcomes (EPIC question nos. 5 and 18). The biochemical recurrence (BCR) rate was defined as two consecutive PSA levels of > 0.2 ng/mL after RARP. Outcomes included in the analysis of the pentafecta rate were complications and positive surgical margins combined with the three outcomes classically reported in the trifecta. Only patients who successfully met all criteria were considered to have reached the pentafecta. Success in each of the parameters was defined as absence of perioperative complications (grade 0 on Clavien-Dindo grading) [6], negative surgical margins, and achievement of composite trifecta outcomes [7]. A nerve-sparing (NS) procedure was attempted in 100 (34.4%) patients. We defined grades two or more as based on the grading system proposed by Tewari et al. [8]. We did not routinely provide postoperative plan for gaining continence and erection to all patients after surgery.

The research protocol was approved by the Institutional Review Board of Hiroshima University Hospital (IRB No. 255). Informed consent has been confirmed by the IRB. The research data were analyzed according to each procedure and risk classification using the chi-squared test and the Mann – Whitney U test. Each analysis we performed had two tails. For all tests, a p value < 0.05 was considered statistically significant. The survey data were analyzed using the chi-squared test (JMP version 15; SAS Institute, Cary, NC, USA).

Results

Demographic characteristics

Table 1 summarizes the patient characteristics and surgical outcomes. The patients' age was significantly lower in the NS group than in the non-NS group ($p = 0.0013$). The ratio of high risk was significantly lower in the NS group than in the non-NS group ($p = 0.0001$). There were no patients were taking phosphodiesterase type 5 inhibitors (PDE5i) before or after surgery.

Longitudinal evaluation of trifecta outcome according to NS procedure

Of the 291 enrolled subjects, 291, 221, 198, 198, and 197 completed questionnaires at preoperative and at 3, 6, 9, and 12 postoperative months, respectively. Trifecta was achieved in 4.6, 5.6, 8.1, and 9.6% of all patients at 3, 6, 9, and 12 months, respectively. Trifecta rates in the NS group were gradually improved to 12.5, 12.7, 18.9, and 23.6% at 3, 6, 9, and 12 months, respectively. In contrast, trifecta rates in the non-NS group were extremely low and had no change with 0.0, 1.6, 1.6, and 2.4%, respectively. There was significant difference at all postoperative points. The number of the patient was 29 in bilateral NS and 71 in unilateral NS. We compare trifecta rates by type of NS, trifecta rates in the bilateral NS group were significantly higher than in the unilateral NS group at all postoperative points (Fig. 1).

Longitudinal evaluation of pentafecta outcome according to NS procedure

Pentafecta was achieved in 2.3, 3.0, 5.1, and 6.1% of all patients at 3, 6, 9, and 12 months, respectively. Pentafecta rates in the NS group were gradually improved to 6.3, 7.0, 10.8, and 13.9% at 3, 6, 9, and 12 months, respectively. In contrast, trifecta rates in the non-NS group were extremely low and had no change with 0.0, 0.8, 1.6, and 1.6%, respectively. Similar trend was showed in the analysis of pentafecta outcome just like trifecta outcome (Fig. 1).

Longitudinal evaluation of trifecta outcome by category according to NS procedure

When we analyzed each category of trifecta outcome, overall, BCR-free rates maintained a high level longitudinally with rates of 94.4, 93.9, 93.9, and 90.9%, respectively. The

Table 1 Patient characteristics

Characteristics	Overall	Nerve sparing (+)	Nerve sparing (−)	*P* value
No. of patients	291	100	191	
Age, year, mean	66.2	64.5	67.1	0.0013
Body mass index, kg/m^2, mean	23.4	23.4	23.4	0.9516
Serum PSA at diagnosis, ng/ml	8.67	6.77	9.67	0.0005
Prostate volume, mL, mean	30.2	30.9	29.8	0.5548
Pathological T stage, *n* (%)				
pT2	230 (79)	92 (92)	138 (72)	0.0002
pT3a	47 (16)	6 (6)	41 (21)	
pT3b	14 (5)	2 (2)	12 (6)	
Pathological grade group, *n* (%)				
1	18 (6)	12 (12)	6 (3)	0.0001
2–3	197 (69)	79 (79)	118 (63)	
4–5	72 (25)	9 (9)	63 (34)	
Risk class, *n* (%)				
Low	46 (16)	26 (26)	20 (10)	0.0001
Intermediate	151 (52)	68 (68)	83 (43)	
High	94 (32)	6 (6)	88 (46)	
Operative time, min, mean	206.5	205.8	206.9	0.8654
Estimated blood loss, mL, mean	190.8	244.3	162.8	0.0008
Positive surgical margin, *n* (%)	76 (26)	24 (24)	52 (27)	0.5502
Pelvic lymph node dissection, *n* (%)	70 (24)	2 (2)	68 (36)	0.0001
Nerve sparing, *n* (%)				
Bilateral		29 (29)		
Unilateral		71 (71)		
Complication, *n* (%)	18 (6)	6 (6)	12 (6)	0.9241

PSA prostate specific antigen

continence rate was improved to 55.2, 75.5, 81.6, and 85.0%. On the other hand, the potency rate was very low, at 7.5, 7.8, 9.8, and 10.9%. Even in the NS group, the BCR-free rate was very high, at 98.6, 98.6, 98.6, and 97.3%, respectively. Continence was sufficiently recovered at 60.0, 81.4, 89.2, and 92.9%. On the other hand, potency rate was gradually improved with 18.1, 18.6, 21.9, and 26.1%, respectively. In the non-NS group, the BCR-free rate was 92.9, 91.9, 91.3, and 86.5%, and continence was recovered at 52.5, 72.2, 77.0, and 77.8%, respectively. The potency rate remained extremely low and almost no change with 0.7, 1.6, 2.5, and 3.2%, respectively (Fig. 2).

Trifecta outcome according to risk classification in NS cases

Our longitudinal analysis suggested the important factor to achieve the trifecta was NS, so next we analyzed trifecta outcome by risk group classification in NS cases. There was almost no change in trifecta outcome in all risk groups, and there was no significant intergroup difference at all postoperative points. We analyzed each category of trifecta, and in all categories, there were no significant differences between each group stratified by D'Amico risk group classifications at all postoperative points (Fig. 3).

Discussion

Widespread PSA screening has resulted in stage migration to PCa, where patients tend to exhibit low grade and low stage PCa [1, 2]. It has also contributed to an increase in DFS, where PSA failure rates over a 5-year period decreased from 14.3 to 2.5% in the early to later PSA era [2]. Furthermore, surgeons are now better able to focus on specific aspects of surgery to maximize continence and potency. RP is associated with high long-term survival rates and the ultimate goal is to maximize QOL and eradicate cancer. Continence and potency are the two most frequent QOL alterations associated with RP [4].

Urinary continence, potency recovery, and lack of BCR represent the trifecta, i.e., the most desired outcomes following RP [9]. These trifecta components represent the most important intermediate and long-term outcomes in patients who have undergone RP to manage PCa [10], and they remain the most relevant for assessing the postoperative

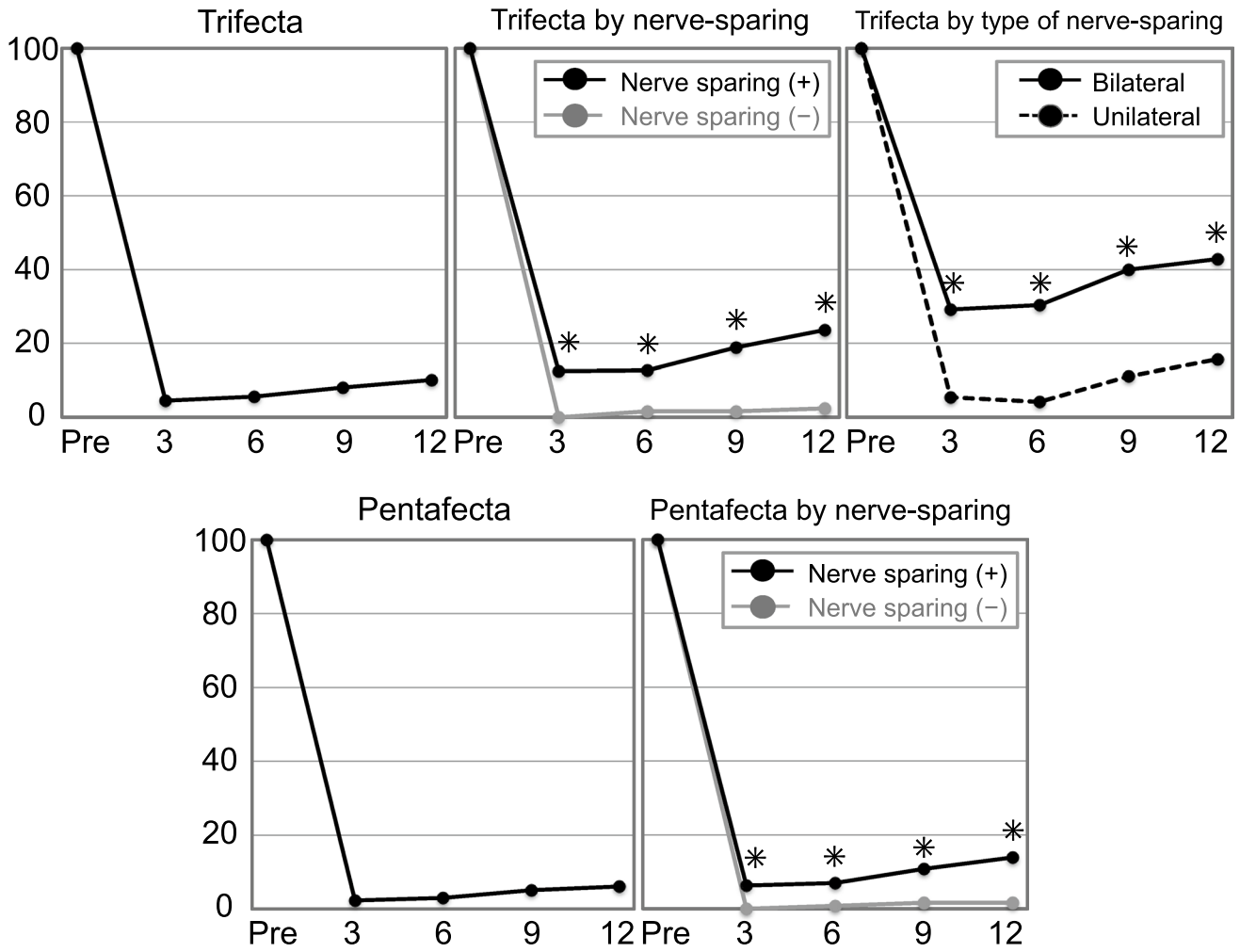

Fig. 1 Trifecta/pentafecta outcome according to nerve-sparing procedure. *$\mathbf{p} < 0.05$

results of RP regardless of the approach used. In general, major RP outcomes are reported separately, and only a few studies have reported the percentage of patients who reach the trifecta [11]. A systematic review showed that the trifecta outcome was achieved in 20–83% of patients, with a mean value of 58% [10]. Such wide variability reflects the heterogeneity of patient characteristics, differing definitions of continence and potency, and follow-up duration. Since cancer recurrence and functional recovery change over time, it can be extremely difficult to evaluate postoperative outcomes. Longitudinal evaluation is considered to have potential for solving problems in the evaluation of trifecta, and this study is the first to longitudinally analyze the trifecta rate of RARP.

Previous studies have utilized several endpoints to evaluate postoperative achievement of the trifecta [7, 10, 12–19]. Erectile function includes several different factors: partial recovery, adequate rigidity, ability for intercourse, and overall sexual satisfaction [4]. Potency has been defined as erection sufficient for intercourse (ESI) with or without use of a PDE5i in many studies [13–18]. Our definition of potency was expanded from only sexual intercourse to sexual activity including masturbation. Our analysis revealed that Japanese PCa patients rarely had sexual intercourse after RARP but had a relatively high frequency of sexual activity including masturbation. Continence has been defined as ‘‘no pad’’ or ‘‘no leak’’ in many studies [18, 19]. However, the use of a safety pad has been accepted as satisfying the achievement of continence in the other studies [2, 15, 16]. Similar to these studies, we define urinary continence as including a safety pad. BCR was assessed with serial serum PSA measurements. The definition of BCR is PSA > 0.2 ng/ml in many studies [7, 10, 12–19].

Our previous longitudinal study showed that sexual function was drastically decreased after RP in Japanese patients with PCa [20]. In the robotic era, more accurate operation and a better surgical field will be possible, so it was expected that widespread use of RARP would improve

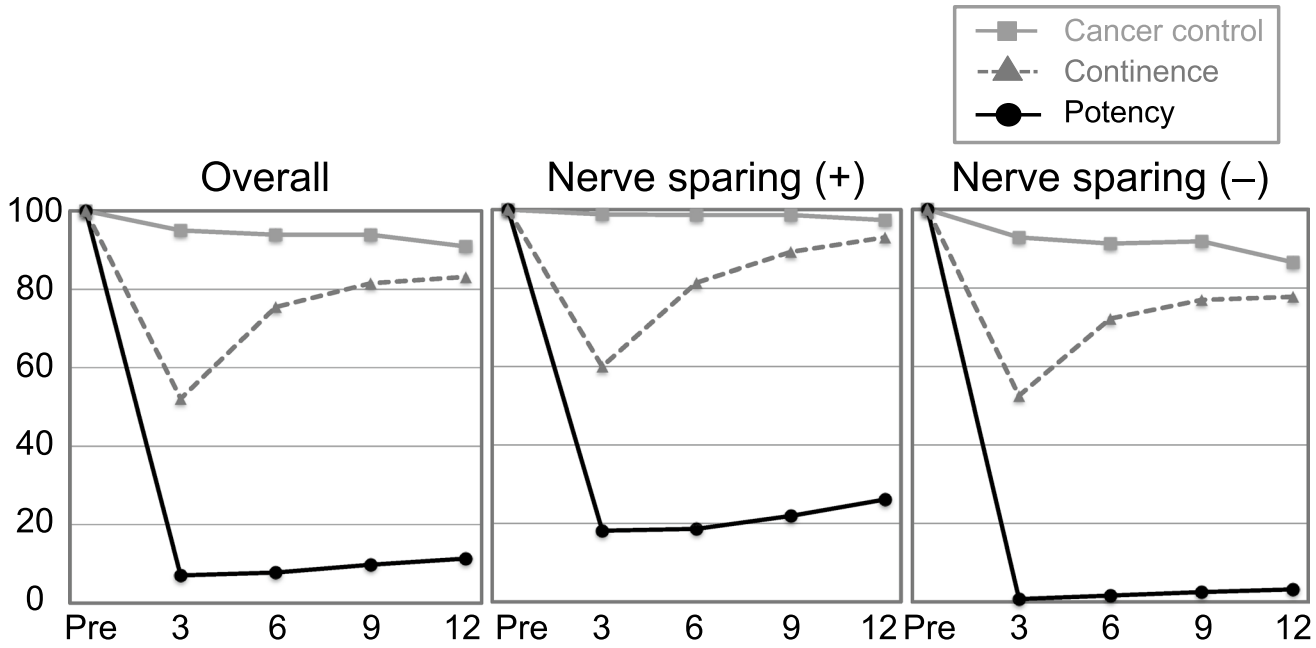

Fig. 2 Trifecta outcome by category according to nerve-sparing procedure

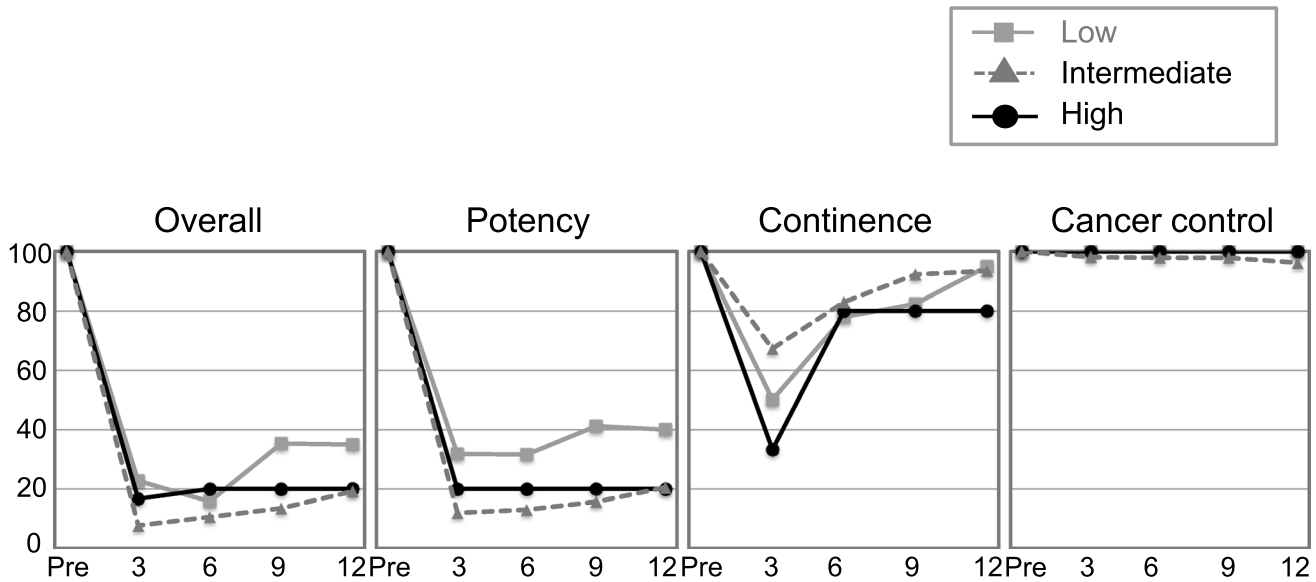

Fig. 3 Trifecta outcome by category according to risk classification in nerve-sparing cases

functional recovery after RP. In this study, the trifecta of 24.6% patients with NS at 12 months was achieved, and it was gradually improved only in the NS patients. Even if patients were treated with RARP, it has become clear that the achievement of trifecta would be almost impossible unless the NS procedure is performed. At 12 months after the image-guided hypofractionated radiotherapy, 57% of the patients met trifecta outcome [21]. Based on these results, focal therapy should be taken into consideration to the patients with PCa in the future.

In Japan, there is a tendency that urologists rarely discuss the patient's sexual life when discussing treatment options for men with localized PCa. Despite previous studies showing a low interest in sex after RP, we found that the assessment of the interest in sex and sexual satisfaction measures over time was important, and this cohort of patients had a high

interest in sex after RP with a significant increase in interest 3–24 months after RP [22]. This may indicate that men shift their focus from survival to continence and potency as they are cured of PCa. Once PCa control is achieved, the patient will focus on continence and potency, so the trifecta represents the best and desired outcomes. Investigations have been reported on individual endpoints, but few studies have addressed these three together [4].

In this study, pentafecta rates maintained a lower level longitudinally than trifecta rate. In the attempt to perform a more comprehensive evaluation of RP outcomes, it was proposed to add postoperative complications and histological margin status to the already established trifecta outcomes [5]. These two additional items added in pentafecta did not show time-dependent changes. Pentafecta outcomes more accurately reflect patient expectations following surgery for PCa [7]. Further development of the surgical technique in RARP is necessary to improve pentafecta outcome based on our pentafecta results.

There were some limitations in our study. First, the number of NS procedures was just 100 (34.4%), which is a small percentage. Especially in the high-risk group, the NS procedure was rarely performed in our cohort. Second, our investigation revealed that Japanese PCa patients rarely have sexual intercourse after RARP and that their frequency of sexual activity including masturbation was relatively high. Many previous studies have reported that potency was defined as ESI [7, 12–18]. However, the definition of potency in this study was expanded from only sexual intercourse to sexual activity including masturbation, and this definition might be specific. In addition, previous study revealed that Japanese men were less likely bothered by sexual function, despite having a lower frequency of erections than American men [23]. These reports indicate that fundamental and cultural differences need to be considered when assessing ED [24]. Third, this is a single center and single surgeon study in only Japanese population, so this may not be applicable to other population. Forth, this study lacks long-term follow-up and a longer follow-up is needed in PCa studies.

The achievement of trifecta is the most desirable outcome after RP. Patients' and surgeons' perceptions and expectations may have an impact on what is reported. Appropriate preoperative counseling should focus on the probability of achieving the trifecta in patients undergoing RP [4]. Our longitudinal evaluation revealed that the achievement rate of trifecta in Japanese patients was very low against all expectations, and potency rate was found to be associated with the achievement of trifecta.

Conclusion

We have proposed a more precise approach for determining outcomes following RP whereby longitudinal evaluation of the trifecta rates is performed. We believe that trifecta outcomes more accurately reflect patients' expectations after RP. This approach may be beneficial and should be used when counseling patients with clinically localized PCa. In our single-surgeon experience, the longitudinal evaluation revealed a low rate of the trifecta in Japanese PCa patients. Further studies of longer duration in which more patients are analyzed will be necessary to validate the current observations using postoperative trifecta outcome.

Author contributions SI: project development, data collection, data analysis, management of patients and manuscript writing. KH: data collection. TH: data analysis. JT: data analysis**,** AM: manuscript editing.

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Compliance with ethical standards

Conflict of interest None of the authors of this study has conflicts of interest or financial disclosures to report.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The research protocol was approved by the Institutional Review Board of Hiroshima University Hospital (No. 255).

Informed consent Informed consent was obtained from all individuals participating in the study.

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