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Original Article

Robot-assisted radical prostatectomy versus volumetric modulated arc therapy: Comparison of front-line therapies for localized prostate cancer

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ABSTRACT

Background: Although radical prostatectomy and external beam radiotherapy are recognized as comparable treatment options for localized prostate cancer, robot-assisted radical prostatectomy (RARP) and volumetric modulated arc therapy (VMAT) as the leading respective techniques have yet to be compared.
Methods: We retrospectively analyzed 860 patients with cT1-4N0M0 prostate cancer who underwent RARP ($n = 500$) or VMAT ($n = 360$) between 2011 and 2016. Biochemical recurrence-free survival (bRFS; two consecutive prostate-specific antigen measurements $\geq$0.2 ng/ml for RARP and Phoenix definition for VMAT) and radiological recurrence-free survival (rRFS; radiologically diagnosed distant metastasis or local recurrence) were compared between the two modalities. Cox proportional hazards model was used for multivariate analysis.
Results: The median follow-up durations were 30 and 47.5 months, and median ages were 67 and 71 years (both $P < 0.0001$) in the RARP and VMAT groups, respectively. VMAT patients had significantly better bRFS than RARP patients, though their definitions of biochemical recurrence differed. If a unified definition of biochemical recurrence (two consecutive prostate-specific antigen measurements $\geq$0.2 ng/ml) was applied, RARP patients had significantly better bRFS than VMAT patients. Regarding rRFS, RARP patients had significantly better outcomes than VMAT patients, however, multivariate analysis together with D'Amico's risk classification, age-adjusted Charlson's comorbidity index, and concomitant androgen-deprivation therapy, demonstrated no significant difference between RARP and VMAT.
Conclusions: The rRFS outcomes of RARP and VMAT after a medium-term follow-up period were similar, despite their different patient backgrounds. Further studies with a longer follow-up period are needed to compare these techniques in terms of cancer-specific and overall survivals.
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Radical prostatectomy and external beam radiotherapy are currently recognized as comparable treatment options for patients with localized prostate cancer (PC) according to current clinical guidelines [1–3]. Although recent studies have reported the possible superiority of surgery over radiotherapy with regard to long-term survival [4–12], the issue of which treatment is better remains controversial [13–19]. Furthermore, robot-assisted radical prostatectomy (RARP) and volumetric modulated arc therapy (VMAT), as the leading respective techniques, have yet to be compared. The present study aimed to compare the oncological outcomes of RARP and VMAT in patients with localized PC.

Methods and materials

Patients

This retrospective study was approved by the internal institutional review board of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (approval number: 12003). We reviewed 874 patients with PC who underwent either RARP ($n = 500$) or VMAT ($n = 374$) with curative intent at The University of Tokyo Hospital between 2011 and 2016. We excluded 14 patients in the VMAT group, including seven with cN1M0 disease and seven who received VMAT in combination with brachytherapy. We finally retrospectively analyzed 860 patients with cT1-4N0M0 PC who underwent either RARP ($n = 500$) or VMAT ($n = 360$). Patients were stratified according to D'Amico's risk classification [13], and the age-adjusted Charlson's comorbidity index (CCI) was assessed at baseline [20].

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Treatments

The choice of RARP or VMAT was decided by the patient and referring physician, following an explanation of the therapeutic alternatives. Poor surgical candidates and those who preferred radiotherapy to surgery were referred for VMAT.

RARP was performed using the peritoneal approach, as described previously [21,22]. Briefly, the Vattikuti Institute prostatectomy technique [23] was modified using a third arm instead of a second assistant forceps. Lymph node dissections were carried out in patients predicted to have ≥5% lymph node metastasis according to the Japan PC nomogram [24]. Cavernous nerve preservation was carried out in the cancer-negative lobe, but bilateral preservation was limited if the patient's cancer was located in the transitional zone.

VMAT was applied in patients with localized disease with any risk category. Each treatment consisted of a single-arc (from −179° to +179°, clockwise) using 6 MV X-rays. The prescribed dose was 76 Gy in 38 fractions to cover 95% of the planning target volume (D95%), while the dose was limited to 72 Gy in 36 fractions in patients receiving anticoagulants or antiaggregates to prevent rectal bleeding. Neoadjuvant androgen-deprivation therapy (ADT) was delivered for 4–6 months in intermediate-risk patients, and for 6 months in high- and very-high-risk patients. Adjuvant ADT was also administered to appropriate patients for 2–3 years at the attendant physician's discretion.

All patients underwent pretreatment evaluations, including blood tests, chest x-rays, computed tomography, and bone scintigraphy. Post-treatment monitoring was generally performed with routine blood tests including PSA every 1–6 months. With manifestation of biochemical recurrence, metastatic work-up by imaging studies including computed tomography and bone scintigraphy was routinely performed.

Endpoints and statistical analysis

Biochemical recurrence-free survival (bRFS) and radiological recurrence-free survival (rRFS) were compared between the RARP and VMAT groups. Biochemical recurrence was defined as two consecutive prostate-specific antigen (PSA) measurements ≥0.2 ng/ml for RARP [3], and the Phoenix definition (PSA ≥nadir + 2 ng/ml) for VMAT [25], respectively, according to the standard definition of biochemical recurrence for each modality. We also tested a unified definition of biochemical recurrence (two consecutive PSA measurements ≥0.2 ng/ml) to make a fair comparison. Radiological recurrence was defined as radiologically diagnosed distant metastasis or local recurrence. Cancer-specific survival (CSS) and overall survival (OS) were also assessed for reference purposes. The follow-up periods started from the day of surgery in the RARP group and from the start of radiotherapy in the VMAT group. Differences in clinical variables between the groups were tested using the Mann–Whitney *U* test for age, initial PSA, CCI, and follow-up duration, and the χ^2 test for biopsy Gleason score, clinical T stage, and D'Amico's risk classification, respectively. The correlation between D'Amico's risk classification and CCI was assessed using the Steel–Dwass test. Survival curves were generated by the Kaplan–Meier method and compared using log-rank tests. Cox proportional hazard regression model was used for multivariate analysis. All statistical analyses were carried out using JMP Pro version 11.0.0 (SAS Institute, Cary, NC, USA). A value of $P < 0.05$ was considered significant. Follow-up information was obtained as of March 2018.

Results

Patient characteristics

The baseline patient characteristics of the RARP and VMAT groups are summarized in Table 1. The median follow-up durations were 30 (1–82) and 47.5 (1–87) months and the median ages were 67 (47–80) and 71 (44–86) years (both $P < 0.0001$) in the RARP and VMAT groups, respectively. According to the D'Amico classification [13], 14.0%, 56.2%, and 29.8% of patients in the RARP group, and 9.4%, 42.8%, and 47.8% of patients in the VMAT group were classified as low-, intermediate-, and high-risk, respectively ($P < 0.0001$). The median age-adjusted CCIs (i.e. total scores) were 3 (1–7) and 4 (1–11) in the RARP and VMAT groups, respectively ($P < 0.0001$). The median age-adjusted CCIs according to the D'Amico risk classification were 3 (1–7), 3 (1–8), and 4 (1–11), in low-, intermediate-, and high-risk patients, respectively (low *vs* intermediate, $P = 0.2386$; low *vs* high, $P < 0.0001$; intermediate *vs* high, $P = 0.0001$). Regarding concomitant treatments, ADT was significantly more common in the VMAT group (224/360, 62.2%) than in the RARP group (25/500, 5.0%) ($P < 0.0001$). All VMAT patients who underwent ADT received neoadjuvant ADT, which was continued if indicated. Among 25 RARP patients who underwent ADT, three received neoadjuvant ADT and 22 received adjuvant ADT. Furthermore, 30 RARP patients underwent adjuvant radiotherapy, including 12 who received radiotherapy alone and 18 who received

Table 1
Baseline characteristics of patients treated with RARP versus VMAT.

Parameter	RARP (500)	VMAT (360)	*P*-value
Age, years, median (range)	67 (47–80)	71 (44–86)	<0.0001*[a]
Initial PSA, ng/ml, median (range)	7.6 (1.4–71)	8.3 (3.0–173)	0.0001*[a]
Biopsy Gleason's score, no. (%):			0.0049*[b]
6	94 (18.8)	58 (16.1)	
7	284 (56.8)	189 (52.5)	
8	73 (14.6)	51 (14.2)	
9	48 (9.6)	54 (15.0)	
10	1 (0.2)	8 (2.2)	
Clinical T stage, no. (%):			<0.0001*[b]
1c	393 (78.6)	175 (48.6)	
2a	56 (11.2)	28 (7.8)	
2b	23 (4.6)	43 (11.9)	
2c	21 (4.2)	64 (17.8)	
3a	5 (1.0)	33 (9.2)	
3b	2 (0.4)	15 (4.2)	
4	0 (0)	2 (0.6)	
D'Amico's risk classification, no. (%):			<0.0001*[b]
Low	70 (14.0)	34 (9.4)	
Intermediate	281 (56.2)	154 (42.8)	
High	149 (29.8)	172 (47.8)	
Pathological Gleason's score, no. (%)			
6	25 (5.0)		
7	337 (67.4)		
8	55 (11.0)		
9	83 (16.6)		
10	0 (0)		
Pathological T stage, no. (%):			
2a	52 (10.4)		
2b	55 (11.0)		
2c	228 (45.6)		
3a	127 (25.4)		
3b	28 (7.6)		
4	0 (0)		
Adverse pathological features, no. (%)			
Positive margins	108 (21.6)		
pN+	8 (1.6)		
CCI, median (range):			
Comorbidity score	0 (0–3)	0 (0–9)	<0.0001*[a]
Age score	3 (1–4)	4 (1–4)	<0.0001*[a]
Total score (=age-adjusted CCI)	3 (1–7)	4 (1–11)	<0.0001*[a]
Concomitant ADT, no. (%)	25 (5.0)	224 (62.2)	<0.0001*[b]
Follow-up duration, months, median (range)	30 (1–82)	47.5 (1–87)	<0.0001*[a]

RARP, robot-assisted radical prostatectomy; VMAT, volumetric modulated arc therapy; PSA, prostate-specific antigen; CCI, Charlson's comorbidity index; ADT, androgen-deprivation therapy.
*Statistically significant; [a]Mann–Whitney's *U* test; [b]χ^2 test.

adjuvant radiotherapy in combination with ADT (overlapping with adjuvant ADT cases). For reference, of 108 patients who had positive margins after RARP, 22 (20.4%) underwent either neoadjuvant or adjuvant treatment: one had received neoadjuvant ADT, 8 received adjuvant radiotherapy alone, and 13 received adjuvant radiotherapy in combination with ADT, respectively.

Treatment outcomes

According to the standard definitions of biochemical recurrence, VMAT patients had a significantly longer bRFS than RARP patients (log-rank test, $P < 0.0001$) (Fig. 1A). The 5-year bRFS rates were 75.9% in the RARP group and 90.8% in the VMAT group, respectively. In contrast, when a unified definition of biochemical recurrence (two consecutive PSA measurements ≥0.2 ng/ml) was applied, RARP patients had significantly better bRFS than VMAT patients (log-rank test, $P < 0.0001$) (Fig. 1B). The 5-year bRFS rates were 75.9% in the RARP group and 41.4% in the VMAT group, respectively.

With regard to the radiological recurrence, RARP patients had significantly longer rRFS than VMAT patients (log-rank test, $P = 0.0194$) (Fig. 2), with 5-year rRFS rates of 97.8% in the RARP and 91.7% in the VMAT groups, respectively. Regarding the sites of radiological recurrence, two patients in the RARP group had local recurrence, two had lymph node metastases, one had bone metastasis, and one had lung metastasis. Among the VMAT group, three patients had local recurrence, two had lymph node metastases, and four had bone metastases.

Multivariate analyses of bRFS showed that all the selected variables, including treatment modality (RARP *vs* VMAT), D'Amico's risk classification (low *vs* intermediate *vs* high), age-adjusted CCI (continuous), and concomitant ADT (No *vs* Yes) were independent prognostic factors when standard definitions of biochemical recurrence were applied (Table 2A), whereas only treatment modality and concomitant ADT were independent prognostic factors when a unified definition of biochemical recurrence was applied (Table 2B).

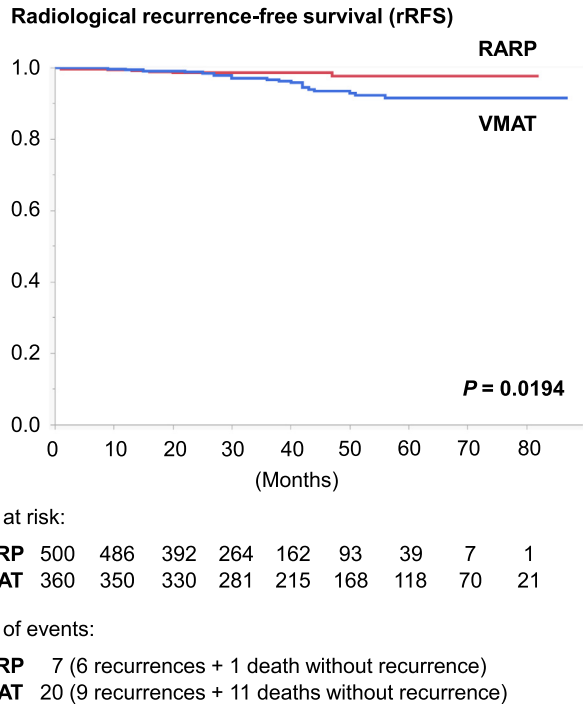

Fig. 2. Kaplan–Meier's curves of RARP versus VMAT patients for radiological recurrence-free survival (rRFS; log-rank test, $P = 0.0194$).

On the other hand, multivariate analysis of rRFS identified age-adjusted CCI as the sole independent predictor of radiological recurrence (HR [95% CI]: 1.40 [1.12–1.72] per score; $P = 0.0039$), with no significant difference in rRFS between RARP and VMAT ($P = 0.9553$) (Table 3).

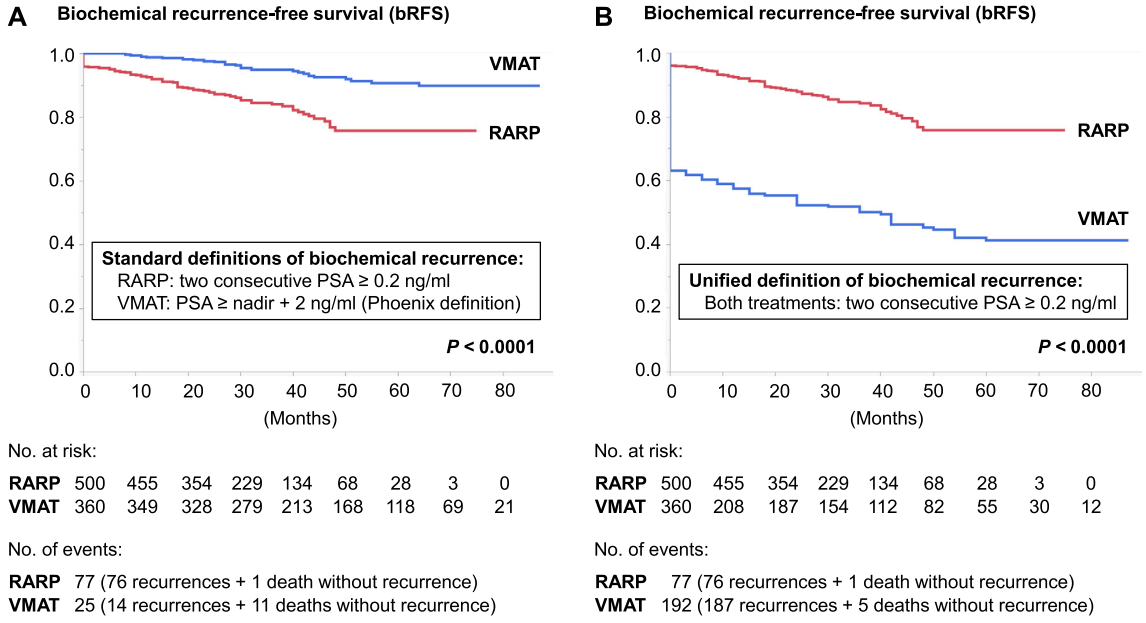

Fig. 1. Kaplan–Meier's curves of RARP versus VMAT patients for biochemical recurrence-free survival (bRFS) using (A) the standard definitions of biochemical recurrence (two consecutive prostate-specific antigen [PSA] measurements ≥0.2 ng/ml for RARP and Phoenix definition for VMAT; log-rank test, $P < 0.0001$) and (B) a unified definition of biochemical recurrence (two consecutive PSA measurements ≥0.2 ng/ml; log-rank test, $P < 0.0001$), respectively.

Table 2
Univariate and multivariate analyses for bRFS.

Parameter (no. of patients)	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
(A) When standard definitions of biochemical recurrence (two consecutive PSA measurements ≥0.2 ng/ml for RARP and Phoenix definition for VMAT) were applied				
Treatment modality		<0.0001*		<0.0001*
RARP (500)	Reference		Reference	
VMAT (360)	0.31 (0.19–0.48)		0.06 (0.03–0.11)	
D'Amico's risk classification		<0.0001*		0.0002*
Low (104)	Reference		Reference	
Intermediate (435)	2.76 (1.11–9.17)	0.0260*	2.78 (1.12–9.27)	0.0246*
High (321)	5.06 (2.08–16.7)	<0.0001*	5.27 (2.11–17.6)	<0.0001*
(High *vs* Intermediate)	1.84 (1.23–2.75)	0.0028*	1.89 (1.23–2.93)	0.0039*
Age-adjusted CCI		0.9502		0.0132*
Continuous (860)	1.00 (0.85–1.15) per score		1.24 (1.05–1.45) per score	
Concomitant ADT		0.8207		<0.0001*
No	Reference		Reference	
Yes	1.05 (0.69–1.57)		4.66 (2.48–8.33)	
(B) When a unified definition of biochemical recurrence (two consecutive PSA measurements ≥ 0.2 ng/ml) was applied.				
Parameter (no. of patients)	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Treatment modality		<0.0001*		<0.0001*
RARP (500)	Reference		Reference	
VMAT (360)	3.75 (2.89–4.92)		6.80 (4.91–9.44)	
D'Amico's risk classification		0.4366		0.7519
Low (104)	Reference		Reference	
Intermediate (435)	1.27 (0.86–1.95)	0.2307	1.15 (0.78–1.77)	0.4888
High (321)	1.15 (0.77–1.78)	0.5133	1.07 (0.69–1.71)	0.7712
(High *vs* Intermediate)	0.90 (0.70–1.16)	0.4272	0.93 (0.68–1.27)	0.6450
Age-adjusted CCI		0.0042*		0.1268
Continuous (860)	1.13 (1.04–1.22) per score		0.93 (0.84–1.02) per score	
Concomitant ADT		0.0198*		<0.0001*
No	Reference		Reference	
Yes	1.35 (1.05–1.72)		0.44 (0.31–0.62)	

bRFS, biochemical recurrence-free survival; PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval; RARP, robot-assisted radical prostatectomy; VMAT, volumetric modulated arc therapy; CCI, Charlson's comorbidity index; ADT, androgen-deprivation therapy.
* Statistically significant.

Table 3
Univariate and multivariate analyses for rRFS.

Parameter (no. of patients)	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Treatment modality		0.0168*		0.9553
RARP (500)	Reference		Reference	
VMAT (360)	2.71 (1.19–6.95)		1.04 (0.31–3.49)	
D'Amico's risk classification		0.0287*		0.4678
Low (104)	Reference		Reference	
Intermediate (435)	1.06 (0.27–7.03)	0.9410	1.05 (0.26–6.96)	0.9535
High (321)	2.96 (0.85–18.6)	0.0956	1.83 (0.49–12.0)	0.4067
(High *vs* Intermediate)	2.79 (1.24–6.84)	0.0127*	1.75 (0.68–4.85)	0.2543
Age-adjusted CCI		0.0001*		0.0039*
Continuous (860)	1.53 (1.25–1.83) per score		1.40 (1.12–1.72) per score	
Concomitant ADT		0.0032*		0.4235
No	Reference		Reference	
Yes	3.17 (1.47–7.21)		1.60 (0.52–5.34)	

rRFS, radiological recurrence-free survival; HR, hazard ratio; CI, confidence interval; RARP, robot-assisted radical prostatectomy; VMAT, volumetric modulated arc therapy; CCI, Charlson's comorbidity index; ADT, androgen-deprivation therapy.
* Statistically significant.

Regarding mortality outcomes, one patient died in the RARP group (postoperative gastric perforation) compared with 14 in the VMAT group (two PC and 12 other causes) (Fig. 3).

Discussion

This study was the first to directly compare the oncological outcomes of RARP and VMAT as the respective front-line surgical and radiotherapy techniques for localized PC. Regarding biochemical recurrence, VMAT demonstrated significantly better bRFS than RARP when standard definitions of biochemical recurrence were used, whereas RARP showed significantly better bRFS than VMAT when a unified definition of biochemical recurrence was applied. Nevertheless, multivariate analysis of rRFS demonstrated no significant difference between RARP and VMAT.

Radical prostatectomy and external beam radiotherapy have been recognized as comparable treatment options for localized PC [1–3]. Several studies, especially earlier studies, have reported the comparabilities of these approaches in terms of both biochemical recurrence [13–15] and cancer-specific and/or overall mortality [16–18]. However, some recent studies have suggested that

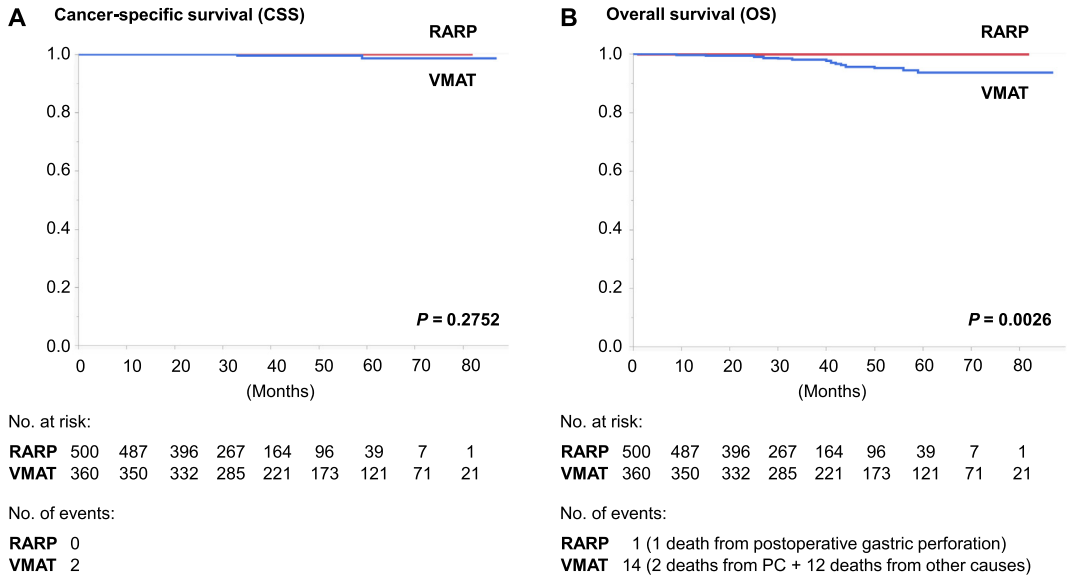

Fig. 3. Kaplan–Meier's curves of RARP versus VMAT patients for (A) cancer-specific survival (CSS; log-rank test, $P = 0.2752$) and (B) overall survival (OS; log-rank test, $P = 0.0026$).

surgery may be associated with a possible survival benefit over radiotherapy, based on long-term observations [4–12], though no studies have yet compared the outcomes of the respective leading techniques, RARP and VMAT. RARP is a novel, gold standard, surgical procedure for the resection of localized PC using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). It has been reported to reduce blood loss, complications, and positive surgical margin rates, resulting in improved safety and feasibility [21,22]. Meanwhile, VMAT represents a sophisticated external beam radiotherapy technique based on rotational intensity-modulated radiotherapy. It delivers a highly conformal beam from a rotating radiation source to the target while avoiding risky organs in a short time, by computerized optimization. It has been reported to reduce complications as well as improve oncologic outcomes [26].

In the present study, bRFS was assessed in two ways: one used the standard definitions of biochemical recurrence; while the other used a unified definition. As shown in Fig. 1 and Table 2, two assessments showed totally opposite results, and both should be cautiously interpreted due to different reasons. The former analysis used different definitions between RARP and VMAT, and thus could count in favor of VMAT. In contrast, the latter analysis was seemingly fair but might have little clinical relevance, because its results should be highly dependent on the concomitant use of ADT especially in VMAT patients. Actually, concomitant ADT use was independently correlated with bRFS based on a unified definition (Table 2B), and therefore, the latter analysis apparently did not reflect the actual clinical situation. Taken together, we deem that results of bRFS should be used for reference purpose only, irrespective of definitions of biochemical recurrence. A unified, clinically relevant definition of biochemical recurrence should be optimized for the better comparison of surgery and radiotherapy [27].

Multivariate analysis of rRFS, a more clinically significant endpoint, showed no significant difference between RARP and VMAT. This seems like a reasonable result given that the actual numbers of patients who experienced radiological recurrence (i.e. excluding those who died without recurrence) were similar in both groups (6/500 [1.2%] in RARP and 9/360 [2.5%] in VMAT). Moreover, the patient backgrounds differed between the groups at baseline, in terms of age, disease stage, comorbidity status, and concomitant ADT use, which might eventually have been adjusted for in the multivariate analysis.

The fact that age-adjusted CCI was identified as a sole independent prognostic factor for rRFS over D'Amico's risk classification was unexpected, but could be explained by frail elderly patients being more susceptible to tumor progression, or presumably having weaker antitumor immunity. Indeed, several previous studies reported that age-adjusted CCI correlated with survival in various malignancies, including PC [28,29]. Similarly, sarcopenia, or age-associated loss of skeletal muscle mass, has recently been reported to correlate with several adverse outcomes in many malignancies [30,31]. Host, as well as tumor factors may play a critical role in antitumor immunity and might thus correlate with the eventual oncological outcomes.

This study was limited by its retrospective design, selection bias, and relatively short follow-up period. As RARP started to be covered by Japanese public health insurance in 2012 and the number of patients receiving RARP gradually increased during the study period (2011–2016), there was a significant difference in follow-up duration between RARP and VMAT, which might hamper the appropriate comparison between the two modalities. Further studies should be conducted to compare more clinically relevant endpoints of CSS and OS between the two treatment options after longer, even follow-up periods. Furthermore, some studies reported that radiotherapy could be more beneficial than surgery in patients with very high-risk PC [19], and radical prostatectomy and external beam radiotherapy should thus be compared in different disease settings.

Lastly, although the present study focused only on oncological outcomes of RARP and VMAT, we also assessed their treatment-related complications. Briefly, major complications of RARP included: 2 (0.1%) rectal injury during surgery, 9 (1.8%) postoperative hemorrhage (Grade $\geq$2) and 5 (1.0%) postoperative additional surgery needed for damage to surrounding organs or abdominal wall hernia, respectively. We have already reported urinary complications after RARP using data on 607 patients including the present 500 cases [32]. Urinary incontinence was seen in 312 of 496 (62.9%) patients at one month after surgery and gradually

decreased to 16 (3.2%) 24 months after surgery. We did not evaluate erectile dysfunction because our cohort had low preoperative IIEF-5 scores. The scores were less than 7 in most cases, whereas median IIEF-5 scores were over 22 in previous studies conducted in Western countries. Meanwhile, major complications of VMAT included: 259 (71.9%) and 47 (13.1%) genitourinary and 52 (14.4%) and 9 (2.5%) gastrointestinal complications (Grade $\geq$1 and $\geq$2) within 6 months of irradiation, and 84 (23.3%) and 34 (9.4%) genitourinary and 45 (12.5%) and 10 (2.8%) gastrointestinal complications (Grade $\geq$1 and $\geq$2) after the 6th month of irradiation, respectively. These treatment-related complications need to be taken into account in the choice of RARP or VMAT as well as their oncological outcomes.

In conclusion, RARP and VMAT may have similar outcomes in terms of radiological recurrence in patients with PC, after medium-term follow-up, after taking account of confounding factors including disease stage, patient age, comorbidity status, and concomitant ADT use. However, further studies with a longer follow-up period are needed to compare these techniques in terms of CSS and OS.

Declaration of Competing Interest

None declared.

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