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Location of Positive Surgical Margin and Its Association With Biochemical Recurrence Rate Do Not Differ Significantly in Four Different Types of Radical Prostatectomy

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Purpose: To analyze the location of the positive surgical margin (PSM) and its association with the biochemical recurrence (BCR) rate in cases of radical prostatectomy (RP) according to the type of surgery.

Materials and Methods: We retrospectively analyzed 1,880 cases of RP. Baseline characteristics were analyzed. Locations of the PSM were recorded in the four surgery groups as apex, anterior, posterolateral, and base and were analyzed by using chi-square test. The association of the location of the PSM with the BCR rate was analyzed by using Kaplan-Meier survival analysis according to the type of surgery, which included radical perineal prostatectomy (RPP, n=633), radical retroperitoneal prostatectomy (RRP, n=309), laparoscopic radical prostatectomy (LRP, n=164), and robot-assisted laparoscopic radical prostatectomy (RALRP, n=774).

Results: A PSM was found in a total of 336 cases (18%): 122 cases of RPP (18%), 67 cases of RRP (17%), 29 cases of LRP (17%), and 119 cases of RALRP (15%). The PSM rate did not differ significantly by surgical type (p=0.142). The location of the PSM was the apex in 136 cases (7.2%), anterior in 67 cases (3.5%), posterolateral in 139 cases (7.3%), and base in 95 cases (5.0%), and showed no significant difference according to surgical type (p=0.536, p=0.557, p=0.062, and p=0.109, respectively). The BCR rate according to the location of the PSM did not differ significantly for the four types of surgery (p=0.694, p=0.301, p=0.445, and p=0.309 for RPP, RRP, LRP, and RALRP, respectively).

Conclusions: The location of the PSM seemed to be unrelated to type of RP. There was no significant correlation between the BCR rate and the location of the PSM for any of the RP types.

Keywords: *Operative surgical procedures; Prostate; Prostate neoplasms; Prostatectomy; Recurrence*

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INTRODUCTION

Radical prostatectomy (RP) is the standard of care among the treatment options for patients with clinically localized prostate cancer, especially in men with a life expectancy > 10 years [1]. A recent RP series reported the positive surgical margin (PSM) rate to range from 11% to 38% [2]. PSM is defined by most investigators as an extension of the tumor to the inked cut surface of the resected specimen [3]. The cause of a PSM is often multifactorial. A PSM is more likely to occur in cases with extracapsular extension, if the prostate is not resected widely enough. A PSM can also occur in cases of organ-confined disease if resection is performed too close to the prostate, which is often referred to

as a capsular incision [4].

A PSM suggests incomplete local resection, poor cancer control, and suboptimal patient outcome [5,6]. In addition, the number and extent of the PSM have been shown to be risk factors for biochemical recurrence (BCR) after RP [7].

Laparoscopic radical prostatectomy (LRP), and more recently robot-assisted laparoscopic radical prostatectomy (RALRP), have been accepted as alternatives to open surgical methods at many institutions [8]. These methods have shown comparable oncological and functional outcomes in recent studies, including for PSM status [9].

When evaluating the efficacy of RP for treating localized prostate cancer and also for considering possible adjuvant therapy, PSM status is an important factor, regardless of approach. Previous data have demonstrated adverse oncologic outcomes associated with PSM in patients undergoing RP [10], although the location of the PSM and its effect on BCR-free survival of RP have rarely been examined in patients who have undergone four different types of RP. In this study, we analyzed the location of the PSM and its association with the BCR rate in patients who had undergone four different types of RP in a single center.

MATERIALS AND METHODS

We retrospectively analyzed the medical records of 1,880 patients who underwent RP between September 1995 and December 2011 by five surgeons at Samsung Medical Center, with approval from the Institutional Review Board (2014-06-049). Among a total of 1,880 patients, 633 patients underwent radical perineal prostatectomy (RPP), 309 patients underwent radical retroperitoneal prostatectomy (RRP), 164 patients underwent LRP, and 774 patients underwent RALRP.

Oncological outcomes were assessed as PSM and BCR rates. The presence of a PSM, age, preoperative prostate-specific antigen (PSA), prostate size, follow-up length, biopsy Gleason score (GS), pathologic GS, clinical stage, pathologic stage, presence of nerve-sparing, and presence of BCR were recorded retrospectively. Locations of the PSM were recorded in the four groups as apex, anterior, posterolateral, and base. All RP specimens were coated with ink, sectioned at 3- to 4-mm intervals, analyzed by the same pathology department, and processed by using the Stanford technique. The surgical margin was considered positive when the tumor was found at the inked surface [11]. Multifocal PSM was defined when a PSM was seen on two or more locations. If the number of PSM locations was ≥2, they were counted separately. Postoperative follow-up visits were typically scheduled at 3-month intervals for 1 year, biannually for the second and third years, and yearly thereafter. Patients without BCR were censored at the last follow-up. BCR was defined as two consecutive PSA measurements ≥ 0.2 ng/mL.

RPP was performed as previously described by Harris [12]. RRP was performed by modified Walsh anatomical RRP. The surgical technique of LRP is described elsewhere

[13]. RALRP was performed by the transperitoneal antegrade approach with the use of the da Vinci Robot System (Intuitive Surgical Inc., Sunnyvale, CA, USA). The choice of surgical approach was made by the patient's physician on the basis of the patient's preference after a discussion of benefits, risks, alternatives, and also the special conditions of each patient. In each of the surgical groups, unilateral or bilateral nerve preservation was considered and performed if clinically indicated by preoperative erectile function, age, and oncological parameters.

The baseline characteristics of the patients were analyzed with percentages for categorical factors or with the mean and standard deviation for continuous factors. Categorical factors were compared by using the chi-square test and Fisher exact test, and continuous factors were compared by using the Kruskal-Wallis test. The estimated risk of BCR according to site of PSM was determined by using Kaplan-Meier survival analysis and was compared by use of log-rank tests. In all of the tests, $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed by using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA) and R ver. 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

RESULTS

The baseline characteristics of the patients are summarized in Table 1. The total number of patients was 1,880, with 633 (33.7%) undergoing RPP, 309 (16.4%) undergoing RRP, 164 (8.7%) undergoing LRP, and 774 (41.2%) undergoing RALRP. There were no significant differences in mean age, PSA level, or prostate size according to operative group (p=0.487, p=0.084, and p=0.389, respectively). The biopsy GS distribution and the clinical stage did not differ significantly by surgical type (p=0.841 and p=0.136, respectively). The pathologic GS distribution and the pathologic stage also did not show a significant difference by surgical type (p=0.783 and p=0.133, respectively).

A PSM was found in a total of 336 cases (17.9%). Of these, there were 122 cases (18.4%) of RPP, 67 cases (21.7%) of RRP, 28 cases (17.1%) of LRP, and 119 cases (15.4%) of RALRP. The PSM rate showed no significant difference by surgical type (p=0.142). The location of the PSM was the apex in 136 cases (7.2%), anterior in 67 cases (3.5%), posterolateral in 139 cases (7.3%), and base in 95 cases (5.0%), and did not differ significantly by surgical type (p=0.536, p=0.557, p=0.062, and p=0.109, respectively) (Table 2).

In all patients, the median follow-up was 48.2 months (interquartile range [IQR], 33.4–64.7 months). The median follow-up of each operative group was 67.7 months (IQR, 40.7–90.9 months) for RPP, 45.9 months (IQR, 32.4–64.4 months) for RRP, 41.4 months (IQR, 27.5–55.8 months) for LRP, and 43.5 months (IQR, 32.4–55.5 months) for RALRP (p < 0.001).

The total number of cases of BCR was 390 (20.7%), with 181 cases (28.5%) in the RPP group, 81 (26.2%) in the RRP group, 24 (14.6%) in the LRP group, and 104 (13.4%) in the

TABLE 1. Characteristics of the study population

Characteristic	Total	RPP	RRP	LRP	RALRP	p-value
No. of patients	1,880 (100)	633 (33.7)	309 (16.4)	164 (8.7)	774 (41.2)	
Age (y)	64.5±6.8	64.2±6.1	65.5±6.6	66.5±6.8	63.9±7.3	0.487
PSA level (ng/mL)	7.7±6.5	8.4±6.8	8.2±7.1	7.1±5.4	7.1±6.2	0.084
Prostate size (mL)	33.2±15.2	33.9±16.0	32.5±15.1	31.4±12.2	33.1±15.1	0.389
Biopsy GS						0.841
≤6	926 (49.2)	301 (47.6)	153 (49.5)	88 (53.7)	384 (49.6)	
7	645 (34.3)	211 (33.3)	112 (36.2)	49 (29.9)	273 (35.3)	
≥8	309 (16.4)	121 (19.1)	44 (14.2)	27 (16.5)	117 (15.1)	
Pathologic GS						0.783
≤6	459 (24.4)	188 (29.7)	82 (26.5)	36 (22.0)	153 (19.8)	
7	1,144 (60.9)	324 (51.9)	185 (59.9)	103 (62.8)	532 (68.7)	
≥8	277 (14.7)	121 (19.1)	42 (13.6)	25 (15.2)	89 (11.5)	
Clinical stage						0.136
≤T2	1,370 (72.9)	523 (82.6)	216 (69.9)	110 (67.1)	521 (67.3)	
T3a	373 (19.8)	58 (9.2)	63 (20.4)	47 (28.7)	205 (26.5)	
T3b	137 (7.3)	52 (8.2)	30 (9.7)	7 (4.3)	48 (6.2)	
Pathologic stage						0.133
≤T2	1,392 (74.0)	513 (81.0)	216 (69.9)	108 (65.9)	555 (71.7)	
T3a	368 (19.6)	86 (13.6)	63 (20.4)	44 (26.8)	175 (22.6)	
T3b	111 (5.9)	30 (4.7)	29 (9.4)	12 (7.3)	40 (5.2)	
T4	9 (0.5)	4 (0.6)	1 (0.3)	0 (0.0)	4 (0.5)	
Nerve saving						<0.001
No	864 (46.0)	369 (58.3)	182 (58.9)	51 (31.1)	262 (33.9)	
Unilateral	412 (21.9)	106 (16.7)	64 (20.7)	29 (17.7)	213 (27.5)	
Bilateral	604 (32.1)	158 (25.0)	63 (20.4)	84 (51.2)	299 (38.6)	
Surgical margins						0.142
Positive	336 (17.9)	122 (18.4)	67 (21.7)	28 (17.1)	119 (15.4)	
Negative	1,544 (80.1)	541 (81.6)	242 (78.3)	136 (82.9)	655 (84.6)	
Follow-up (mo), median (IQR)	48.2 (22.7)	67.7 (27.2)	45.9 (25.8)	41.4 (18.7)	43.5 (16.8)	<0.001
BCR						<0.001
No	1,490 (79.2)	452 (71.4)	228 (73.7)	140 (85.3)	670 (86.5)	
Yes	390 (20.7)	181 (28.5)	81 (26.2)	24 (14.6)	104 (13.4)	

Values are presented as number (%) or mean±standard deviation unless otherwise indicated.

RPP, radical perineal prostatectomy; RRP, radical retroperitoneal prostatectomy; LRP, laparoscopic radical prostatectomy; RALRP, robot-assisted laparoscopic radical prostatectomy; PSA, prostate-specific antigen; GS, Gleason score; IQR, interquartile range; BCR, biochemical recurrence.

TABLE 2. Location of PSM according to type of surgery

Location	Total	RPP	RRP	LRP	RALRP	p-value
Apex	136 (7.2)	45 (7.1)	24 (7.7)	16 (9.7)	51 (6.5)	0.536
Anterior	67 (3.5)	19 (3.0)	9 (2.9)	6 (3.6)	33 (4.2)	0.557
Posterolateral	139 (7.3)	64 (10.1)	27 (8.7)	7 (7.0)	41 (5.3)	0.062
Base	95 (5.0)	28 (4.4)	24 (7.7)	9 (5.4)	34 (4.3)	0.109

Values are presented as number (%).

PSM, positive surgical margin; RPP, radical perineal prostatectomy; RRP, radical retroperitoneal prostatectomy; LRP, laparoscopic radical prostatectomy; RALRP, robot-assisted laparoscopic radical prostatectomy.

RALRP group. Cases with a PSM showed a higher BCR rate than did cases with a negative surgical margin (p=0.04). In the PSM group, the BCR rate did not differ significantly according to the location of the PSM in all RP groups combined (p=0.469). The BCR rate according to the location of the PSM also did not show a significant difference in the Kaplan-Meier survival analysis for the four types of sur-

gery (p=0.694, p=0.301, p=0.445, and p=0.309 for RPP, RRP, LRP, and RALRP, respectively) (Fig. 1). The site of the PSM was not an independent predictor of BCR.

DISCUSSION

Yossepowitch et al. [2] demonstrated that a PSM in RP

A

RP

PSM site
— Apex
-- Anterior
···· Posterolateral
-·- Base
-··- Multifocal

Log-rank test, p=0.469

BCR-free survival (%) vs Time from surgery (mo)

B

RPP

PSM site
— Apex
-- Anterior
···· Posterolateral
-·- Base
-··- Multifocal

Log-rank test, p=0.694

BCR-free survival (%) vs Time from surgery (mo)

C

RRP

PSM site
— Apex
-- Anterior
···· Posterolateral
-·- Base
-··- Multifocal

Log-rank test, p=0.301

BCR-free survival (%) vs Time from surgery (mo)

D

LRP

PSM site
— Apex
-- Anterior
···· Posterolateral
-·- Base
-··- Multifocal

Log-rank test, p=0.445

BCR-free survival (%) vs Time from surgery (mo)

E

RALRP

PSM site
— Apex
-- Anterior
···· Posterolateral
-·- Base
-··- Multifocal

Log-rank test, p=0.309
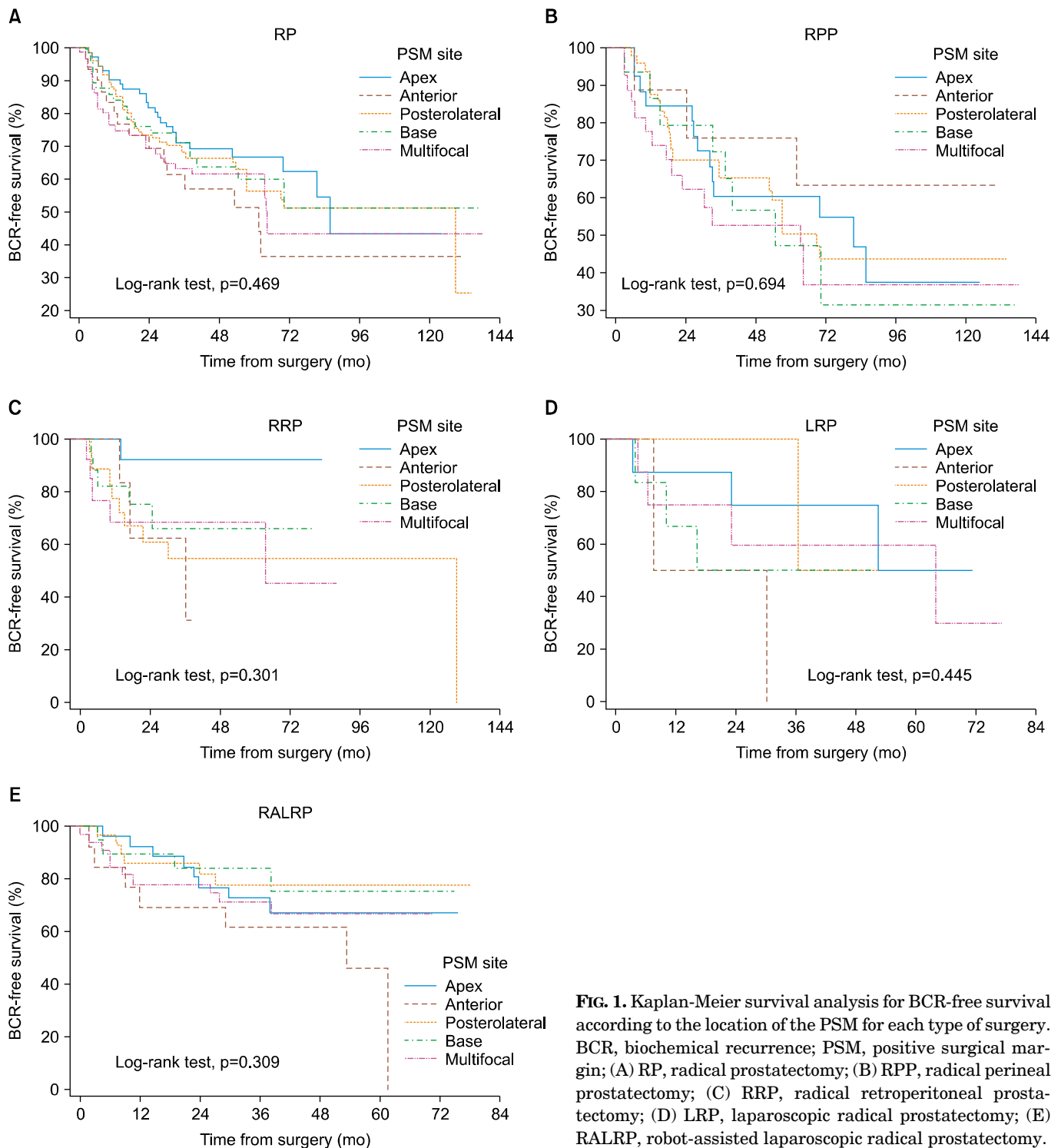
BCR-free survival (%) vs Time from surgery (mo)

FIG. 1. Kaplan-Meier survival analysis for BCR-free survival according to the location of the PSM for each type of surgery. BCR, biochemical recurrence; PSM, positive surgical margin; (A) RP, radical prostatectomy; (B) RPP, radical perineal prostatectomy; (C) RRP, radical retroperitoneal prostatectomy; (D) LRP, laparoscopic radical prostatectomy; (E) RALRP, robot-assisted laparoscopic radical prostatectomy.

specimens is an adverse outcome following RP. Pathologic tumor margin status seems to be comparable between open, laparoscopic, and robotic series overall [14]. However, the location of the PSM and its effect on BCR-free survival of RP has rarely been examined among patients according to four different types of RP in a single center. Therefore, we explored the location of the PSM and its association with the BCR rate between four different types of RP. We found that the location of the PSM seemed to be un-

related to the type of RP. In addition, the BCR rate did not differ significantly according to the location of the PSM in each type of RP.

In one retrospective study, there was no significant difference in the incidence of a PSM between the RPP (22%) and RRP specimens (16%), and each had a 4% incidence of capsular incision [15]. Moreover, no significant difference was found in the time to PSA failure between patients who had undergone RPP with complete excision of the seminal

vesicles and those who had undergone RRP [16]. RPP showed proven long-term cancer control of RRP with rapid convalescence and low morbidity [12,17-19]. In a retrospective comparison of BCR, no significant difference was found between the RALRP group and a contemporary series of RRP performed at a single center after control for clinical and pathologic features [20]. In most series of LRP and RALRP, PSM percentages decrease with experience [9,21].

Touijer et al. [22] showed that regardless of surgical approach, the most common site of a PSM is the prostatic apex and that insufficient removal of prostatic tissue at the apex for optimizing urethral length and avoiding incontinence can result in PSMs, even with tumors that do not violate the capsule pathologically (i.e., stage pT2). In addition, Brown et al. [23] and Khan and Partin [24] demonstrated that comparison of surgical margin status between high-volume centers with operations performed by experienced surgeons shows a definitive advantage in achieving negative surgical margins for one surgical approach over the other. These results differ from the results of our study, most likely due to differences in patient selection. Patient selection is the primary factor that determines the PSM rate in a given series. The experience of surgeons and the method and detail of pathologic analysis also seems influential.

Although this study was retrospective and was performed at a single institution, this enabled a standardized review of all pathology specimens of the four different types of RP and strengthened our study. This study was limited by the difference in follow-up length according to type of surgery. The BCR rate of LRP or RALRP was relatively low compared with the BCR rate for RPP or RRP. The median follow-up and BCR rate according to type of surgery showed statistically significant differences ($p < 0.001$ and $p < 0.001$, respectively) (Table 1). Therefore, the tendency of a higher BCR rate of RPP or RRP may come from the relatively shorter follow-up of LRP or RALRP.

Oncologic outcomes with 1,000 consecutive LRPs performed over a 4-year period with a median follow-up period of 12 months were reported by Guillonneau et al. [25]. Their overall actuarial BCR-free survival rate was 90.5% at 3 years. The rates were 92% for pT2a, 88% for pT2b, 77% for pT3a, and 44% for pT3b by pathologic stage. Pavlovich et al. [26] reported on 528 consecutive LRPs with a mean follow-up of 13 months. The actuarial, 3-year, BCR-free survival was 94.5% overall, 98.2% for pT2, and 78.7% for pT3 disease. These two studies of LRP reported better BCR-free survival than did our study (89.7%). This difference in BCR-free survival may be due to the shorter mean follow-up length of those studies compared with our study. Meanwhile, with regard to RALRP, Badani et al. [27] reported a large series of 2,766 consecutive RALRPs with a mean follow-up period of 22 months. Their overall actuarial 5-year, BCR-free survival was 84% overall, 84% for pT2, and 66% for pT3 patients, which was a worse BCR-free survival than in our study (90.3%). This difference may be due to the shorter mean follow-up length of our study compared

with the study of Badani et al. [27].

Because of the relatively long time period included in this study, the learning curve with surgery or progression of surgical technique may have had an effect. Especially, RALRP is a relatively newer method, so the learning curve may have influenced oncologic outcome. Meanwhile, RP was performed by five surgeons in this study. Each method of RP was performed by more than one surgeon, except RPP and LRP. Despite this limitation, considering the lack of cases when performing four types of RP in a single center, this study offers a valuable comparison of the different types of RP.

In summary, the location of the PSM does not seem to be related to the type of RP. The BCR rate according to the location of the PSM in each type of RP also showed no significant difference. In the end, a long-term, prospective and randomized trial with a sufficiently large number of cases from established and experienced centers of excellence is required to compare the results of LRP or RALRP with the results of RPP or RRP.

CONCLUSIONS

In this study, we presented the oncologic outcomes in a large contemporary cohort of patients undergoing four different types of RP. Location of the PSM was not related to type of RP. The BCR rate also showed no significant difference according to the location of the PSM in each type of RP.

CONFLICTS OF INTEREST
The authors have nothing to disclose.

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