We report the overall rate, locations and predictive factors of positive surgical margins (PSMs) in 271 patients with high-risk prostate cancer. Between April 2008 and October 2011, we prospectively collected data from patients classified as D’Amico high-risk who underwent robot-assisted laparoscopic radical prostatectomy. Overall rate and location of PSMs were reported. Stepwise logistic regression models were fitted to assess predictive factors of PSM. The overall rate of PSMs was 25.1% (68 of 271 patients). Of these PSM, 38.2% (26 of 68) were posterolateral (PL), 26.5% (18 of 68) multifocal, 16.2% (11 of 68) in the apex, 14.7% (10 of 68) in the bladder neck, and 4.4% (3/68) in other locations. The PSM rate of patients with pathological stage pT2 was 8.6% (12 of 140), 26.6% (17 of 64) of pT3a, 53.3% (32/60) of pT3b, and 100% (7 of 7) of pT4. In a logistic regression model including pre-, intra-, and post-operative parameters, body mass index (odds ratio [OR]: 1.09; 95% confidence interval [CI]: 1.01–1.19, P = 0.029), pathological stage (pT3b or higher vs pT2; OR: 5.14; 95% CI: 1.92–13.78; P = 0.001) and percentage of the tumor (OR: 46.71; 95% CI: 6.37–342.57; P < 0.001) were independent predictive factors for PSMs. The most common location of PSMs in patients at high-risk was the PL aspect, which reflects the reported tumor aggressiveness. The only significant predictive factors of PSMs were pathological outcomes, such as percentage of the tumor in the specimen and pathological stage. 

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Keywords: prostate; prostatectomy; prostatic neoplasm; residual; robotics

INTRODUCTION

Growing evidence supports the need for observation or active surveillance of men with localized prostate cancer (PCa), especially those who are at low clinical risk. In contrast, contemporary studies support a trend toward performing radical prostatectomy (RP) in men with high-risk PCa given their favorable results. Reports of RP in patients at high-risk is not new, but high-quality evidence of the merits of surgery has not been reported. Therefore, the merits of surgery in patients at high-risk with PCa remain debatable and many treatment options exist. Lawrentschuk et al. noted that the life expectancy of the patient, the characteristics and the curability of the cancer, and the morbidity of treatment should all be considered when selecting the best treatment option.

The role of RP in patients at high-risk is part of a multimodal approach, although a significant number of patients undergo surgery as a monotherapy. Modalities that do not include organ removal cannot accurately determine tumor characteristics, such as grade and stage, and eventual prognosis. Although the D’Amico classification is generally used to predict patient prognosis preoperatively, the aggressiveness of PCa can be more precisely evaluated from RP specimens. These pathological outcomes are useful in planning the optimal additional local treatment strategies.

The morbidity of robot-assisted laparoscopic radical prostatectomy (RALP) for most men is comparable to RT another treatment option in patients at high-risk. RALP arguably decreases complications, blood transfusions, and lengths of stay. Although no randomized trial has compared open RP and RALP, the increased use of robots corresponds with decreasing morbidity. A recent comparative study assessing >7000 men reported that patients with high-risk PCa had lower mortality when treated with RP than with radiation or androgen-deprivation therapy alone. RALP can also achieve a positive surgical margin (PSM) rate equivalent to that of open RP. However, several studies in patients at high-risk have suggested that the PSM rates are too high. They also suggest that open surgery is preferred because the absence of haptic feedback with RALP can result in a high PSM rate. Few studies of RALP have included patients with high-risk PCa and most included a small number of patients. The current study includes 271 men with high-risk PCa where RALP was performed by a single surgeon. We only included surgeries performed after the surgeon's first 1500 surgeries to minimize...
the effects of the learning curve on the rate, location, and predictive factors of PSMs. We investigated the overall PSM rate and specific PSM locations following robot-assisted radical prostatectomy (RARP). We also determined predictive factors for PSM by evaluating pre-, intra-, and post-operative variables.

**MATERIALS AND METHODS**

**Patient selection**

From 2008 to 2011, 3156 patients underwent RARP performed by a single surgeon (VRP) who had performed more than 1500 such operations. The clinical records of all patients who provided informed consent were prospectively collected and retrospectively analyzed after receiving approval from the Institutional Review Board. Of these men, we identified 271 who met the D’Amico high-risk criteria: prostate-specific antigen (PSA) level > 20 ng ml⁻¹, Gleason score (GS) of 8–10, or clinical stage ≥ T2c.¹ The clinical stage was determined from a thorough examination of the bilateral prostate lobe by digital rectal examination (DRE) under anesthesia. A bone scan was performed on patients with a PSA > 20 ng ml⁻¹, a clinical stage ≥ T3, GS ≥ 8, or clinical symptoms to evaluate metastases. Computed tomography (CT) scans and magnetic resonance imaging (MRI) were not routinely recommended. However, a CT scan was recommended if the clinical stage was ≥ T3 or the PSA level was >10 ng ml⁻¹ in selected patients. All bone scans and pelvic imaging (CT or MRI) in this study were negative for metastases.

**Surgical technique**

All surgical procedures were performed using a transperitoneal, six-port technique as previously reported.¹⁷ This technique is an early retrograde, athermal, interfascial nerve sparing (NS) procedure performed with minimal traction.²¹ After the seminal vesicles were mobilized and the posterior dissection was completed, the procedure usually began at the left side NS. The prostate was axially rotated clockwise and fixed with an assistant microfrance grasper to expose the left lateral aspect of the prostate. An interfascial plane between the neurovascular bundle (NVB) and prostate was developed at the level of the midprostate and dissected posteriorly until it reached the posterior plane of dissection between the prostate and rectum, created previously. The interfascial plane was extended both distally to the apex, and proximally to the prostatic pedicle. At this stage, the nerve bundle was only attached to the prostate by the pedicle. The pedicle was divided athermally after applying hemolock clips. A few millimeters of space was usually created between the NVB and the base of the prostate to safely apply the clips. The NS on the right side was then replicated in a similar fashion. The full surgical technique is well described in our previous reports.

A certain degree of NS was generally attempted in all patients. The indication for partial versus full NS is not clearly described in previous reports.²⁴ From 2008 to 2011, 3156 patients underwent RARP performed by a single surgeon (VRP) who had performed more than 1500 such operations. The clinical records of all patients who provided informed consent were prospectively collected and retrospectively analyzed after receiving approval from the Institutional Review Board. Of these men, we identified 271 who met the D’Amico high-risk criteria: prostate-specific antigen (PSA) level > 20 ng ml⁻¹, Gleason score (GS) of 8–10, or clinical stage ≥ T2c. The clinical stage was determined from a thorough examination of the bilateral prostate lobe by digital rectal examination (DRE) under anesthesia. A bone scan was performed on patients with a PSA > 20 ng ml⁻¹, a clinical stage ≥ T3, GS ≥ 8, or clinical symptoms to evaluate metastases. Computed tomography (CT) scans and magnetic resonance imaging (MRI) were not routinely recommended. However, a CT scan was recommended if the clinical stage was ≥ T3 or the PSA level was >10 ng ml⁻¹ in selected patients. All bone scans and pelvic imaging (CT or MRI) in this study were negative for metastases.

**RESULTS**

Table 1 shows the basic characteristics of the 271 evaluated patients. The mean age was 62.9 years (range, 40.0–80.0), and the mean BMI was 28.6 kg m⁻² (range, 21.0–41.0). The mean preoperative PSA level was 9.9 ng ml⁻¹ (range, 1.5–71.0), and the mean prostate weight was 53.0 g (range, 24.0–135.0). The clinical stages were as follows: 121 (44.6%) with T1c, 126 (46.5%) with T2, and 19 (7.0%) with T3 or higher. Biopsy GSs were 6 in 13 patients (4.8%), 7 in 26 patients (9.6%), and 8 or higher in 232 patients (85.6%). Pathologic positive surgical margins after robot-assisted radical prostatectomy

**Table 1: Patient characteristics**

| Characteristics                      | n=271 |
|--------------------------------------|-------|
| Age, year, median (IQR)              | 62.9 (40.0–80.0) |
| BMI, kg m⁻², median (IQR)             | 28.6 (21.0–41.0) |
| Preoperative PSA level, ng ml⁻¹, median (IQR) | 9.9 (1.5–71.0) |
| Prostate weight, g, median (IQR)      | 53.0 (24.0–135.0) |
| Clinical stage, n (%)                 |       |
| T1c                                  | 121 (44.6) |
| T2                                   | 126 (46.5) |
| T3                                   | 19 (7.0)  |
| Biopsy Gleason score, n (%)           |       |
| ≤ 6                                  | 13 (4.8)  |
| 7                                    | 26 (9.6)  |
| ≥ 8                                  | 232 (85.6) |
| Pathologic stage, n (%)               |       |
| pT2                                  | 140 (51.7) |
| pT3a                                 | 64 (23.6) |
| pT3b                                 | 60 (22.1) |
| pT4                                  | 7 (2.6)   |
| Pathologic Gleason score, n (%)       |       |
| ≤ 6                                  | 22 (8.1)  |
| 7                                    | 138 (50.9) |
| ≥ 8                                  | 111 (41.0) |

BMI: body mass index; PSA: prostate-specific antigen; IQR: interquartile range
Table 2: PSM rate and site-specific PSM rate by pathological stage

| Pathological stage | Total (%) |
|--------------------|-----------|
| T2 (%)             | 140 (51.7) |
| T3a (%)            | 64 (23.6)  |
| T3b (%)            | 60 (22.1)  |
| T4 (%)             | 7 (2.6)    |

stages were T2 in 140 patients (51.7%), T3a in 64 patients (23.6%), T3b in 60 patients (22.1%), and T4 in 7 patients (2.6%). Pathological GSs were 6 in 22 patients (8.1%), 7 in 138 patients (50.9%), and 8 or higher in 111 patients (41.0%).

The overall PSM rate was 25.1% (68 of 271 patients). The PSM rate of patients with pathological stage pT2 was 8.6% (12 of 140), 26.6% (17 of 64) of pT3a, 53.3% (32/60) of pT3b, and 100% (7 of 7) of pT4. Of the PSMs, 38.2% (26 of 68) were PL, 26.5% (18 of 68) were MF, 16.2% (11 of 68) were apical, 14.7% (10 of 68) were in the BN, 2.9% (2 of 68) were in the anterior prostate, and 1.5% (1/68) were in the vas deferens. In pT2 specimens, 41.7% of PSMs were located at the apex and 41.7% were PL. In pT3a and pT3b specimens, the most common PSM site was PL (41.2% and 40.6%, respectively), and the most common PSM site in pT4 specimens was MF (42.9%) (Table 2).

Table 3 shows the association between pre-, intra-, and post-operative parameters and PSMs by univariate analysis. Preoperative PSA and clinical stage were predictors of PSM (P = 0.045 and P = 0.040, respectively). Among patients with pT2 and pT3 tumors, the PSM rates were similar regardless of the type of NS procedure performed (P = 0.996 and P = 0.130, respectively). Pathological stage, pathological GS, and percentage of tumor were associated with an increased risk of PSM (P < 0.001, P = 0.048, and P < 0.001, respectively).

In the multiple logistic regression model that included only preoperative parameters, preoperative PSA and clinical stage were independent predictive factors for PSMs. A clinical stage of T3 or higher was associated with a 4.43-fold higher-risk of PSM than was a stage of T1c (95% confidence interval [CI]: 1.55–12.71). Preoperative PSA was also significantly associated with PSMs in this model (odds ratio [OR]: 1.03; 95% CI: 1.00–1.05, P = 0.042). In the logistic regression model that included pre-, intra-, and post-operative parameters, BMI, pathological stage, and the percentage of tumor were independent predictive factors for PSM. A pathological stage of T3b or higher was associated with a 5.14-fold higher-risk of PSM than was stage of pT2 (95% CI: 1.92–13.78). BMI was also associated with PSMs by multivariate analysis (OR: 1.09; 95% CI: 1.01–1.19, P = 0.029). The percentage of tumor in the surgical specimen was the most significant predictor of a PSM in the multivariate analysis (OR: 46.71; 95% CI: 6.37–342.57; P < 0.001) (Table 4).

DISCUSSION

Men with high-risk localized PCa require active treatment, but no consensus regarding the optimal treatment has been reached.16,18 When selecting treatments for these patients, several factors should be considered such as the patient’s age, the natural history of the PCa, the curability of the disease, and treatment morbidities such as continence.8 Although RP has been performed in patients at high-risk, surgery is less frequently performed in these patients because of the known risk of

Table 3: Association between preoperative, intraoperative, and postoperative parameters with PSMs: univariate analysis

| Parameters | Margin status | P |
|------------|---------------|---|
| Preoperative parameters | | |
| Age, year, mean±s.d. | 63±7.1 | 61±7.2 | 0.212 |
| BMI, kg m⁻², mean±s.d. | 28±4.3 | 29±4.4 | 0.180 |
| PSA, ng ml⁻¹, mean±s.d. | 9.0±9.3 | 12.0±12.2 | 0.045 |
| Clinical stage, n (%) | | | |
| T1c | 95 (78.5) | 26 (21.5) | | |
| T2 | 93 (73.8) | 33 (26.2) | | |
| T3 | 10 (52.6) | 9 (47.4) | | |
| <0.001 | | | |
| Biopsy Gleason score, n (%) | | | |
| ≤6 | 11 (84.6) | 2 (15.4) | | |
| 7 | 17 (65.4) | 9 (34.6) | | |
| ≥8 | 175 (75.4) | 57 (24.6) | | |
| 0.388 | | | |
| Intraoperative parameters | | | |
| Type of nerve sparing, n (%) | | | |
| pT2 | | | | |
| NNS | 21 (100.0) | 0 (0.0) | | |
| UNS | 8 (88.9) | 1 (11.1) | | |
| PNS | 68 (89.5) | 8 (10.5) | | |
| BNS | 30 (90.9) | 3 (9.1) | | |
| 0.788 | | | | |
| <0.001 | | | | |
Table 4: Multivariate analysis of independent predicting factors of PSMs

| Variable                      | OR (95% CI) | P     |
|-------------------------------|-------------|-------|
| Only preoperative variables   |             |       |
| BMI                           | 1.06 (1.00–1.14) | 0.068 |
| PSA                           | 1.03 (1.00–1.05) | 0.042 |
| Clinical stage                |             |       |
| T1c versus T2                 | 1.50 (0.82–2.77) | 0.191 |
| T1c versus T3                 | 4.43 (1.55–12.71) | 0.006 |
| Pre-, intra-, and postoperative variables combined | 1.09 (1.01–1.19) | 0.029 |
| BMI                           |             |       |
| Pathological stage            |             |       |
| T2 versus T3a                 | 1.63 (0.64–4.12) | 0.302 |
| T2 versus T3b                 | 5.14 (1.96–13.78) | 0.001 |
| Percentage of tumor           | 46.71 (6.37–342.57) | <0.001 |

BMI: body mass index; PSA: prostate specific antigen; OR: odds ratio; CI: confidence interval

disease recurrence. However, the trend toward performing RP in more patients at high-risk is supported by recent reports of favorable results. Surgery is best used as a part of a multimodal approach combining RP, extensive lymphadenectomy, and when required, additional radiation therapy, and hormonal therapy. Although the optimal timing of RT in men with PCa is still controversial, the rationale for offering additional local therapy to men with PCa is generally accepted.

Therefore, knowing the margin status in the patients with high-risk is important to develop an additional treatment plan. Thus, in patients at high-risk, RP can initially be used to cure the cancer or as the first step of a treatment plan to improve pathological outcomes. However, only a few studies have reported PSM rates and factors predictive of PSMs from high-volume centers.

The increasing use of surgery to treat patients at high-risk coincides with the increasing use of minimally invasive RALP. Although the role of RALP in patients at high-risk has not been well described, the purported advantages of a decreased length of stay and earlier return to baseline function correspond with the increased use of RALP. Technical refinement and technological advantages such as three-dimensional vision, magnification, and freedom have contributed to decreases in PSM rates in recent RP series.

Patel et al. reported that the PSM rate for patients with pT2 tumors in a multi-institutional series was lower in the RARP group than in open RP group. The overall PSM rate in patients at high-risk was sparse and highly variable in previous studies. Røder et al. recently reported that the overall PSM rate of RARP was 49.8% in 231 patients at high-risk, but the overall PSM rate reported by Lavery et al. in 123 patients at high-risk was 31%.

In our study, the overall PSM rate was 25% in 271 patients at high-risk. Our data showed that the overall PSM rate of RP performed by an experienced surgeon is excellent regardless of the availability of haptic feedback. However, the PSM rate in patients at high-risk in our study cannot be applied to low-volume centers. Recently, Sooriakumaran et al. reported that PSM rates were highly affected by an individual surgeon's caseload, and previous studies have suggested that 1000–1500 surgeries using a robotic approach are needed to minimize the PSM rate. In our study, a single surgeon who had performed more than 1500 RALP cases performed all of the surgeries. In addition, our study had a high proportion (51.7% in pT2) of organ-confined patients, similar to the previous RARP study that showed low PSM rates.

In our study, the mean PSM rate for pT2 tumors was 8.6% and 39.5% for pT3 tumors. Van der Kwast et al. showed that a PSM was predictive for a better adjuvant RT outcome based on European Organization for Research and Treatment of Cancer. They suggested that immediate postoperative radiotherapy might not be recommended for PCa patients with negative surgical margins. Although the optimal timing of additional local therapy is still controversial and requires results from ongoing prospective randomized studies, PSMs are useful in planning the strategy with multimodal treatments.

Recently, Connolly et al. suggested that RALP should be the first step in a multimodal treatment strategy for men with high-risk PCa. Our results also showed that RARP can be useful for planning additional treatments and may be curative, even in patients at high-risk.

A multivariate analysis that included only preoperative variables showed that PSA levels and clinical stage were independent predictive factors for PSM. However, when considering pre-, intra-, and post-operative variables combined, a clinical stage and PSA were excluded from the predictive factors of PSM. Pathological stage (over pT3b vs pT2 OR: 5.14, 95% CI: 1.96–13.78), the percent of tumor in the surgical specimen (OR: 46.71, 95% CI: 6.37–342.57), and BMI were the only independent predictive factors for PSMs.

Although the percent of tumor was significant and had a high CI, the OR was 46.71 and had a wide CI (6.37–342.57). This outcome might be the result of a relatively small number of events (68) and having eight covariates in multivariate analysis. This result should be verified with a larger number of patients.

The lack of preoperative variables in the multivariate analysis might be explained by the inaccuracy of DRE and high T upstaging. Clinical stage by DRE has had a high rate of upstaging in previous reports. Lavery et al. reported that among 123 patients with high-risk PCa, high T upstaging happened in 4.5%–68% of cases. Similarly, Røder et al. reported T upstaging rates of 11.7%–65.8%. In our study, T upstaging also happened from 7% to 78%. Although only postoperative pathologic variables were included in predicting PSMs, preoperative variables are important in planning which surgical technique to use for each patient and cannot be replaced by postoperative variables. Hence, the lack of accuracy of DRE will need to be reinforced with radiologic evaluations such as multiparametric MRI. Therefore, the importance of preoperative parameters should not be overlooked during preoperative risk stratification. Postoperative variables obtained from RALP are useful in planning additional local treatment strategies in a multimodal approach.

A recent study at our institution investigated factors predictive for PSMs and their location after RALP in 876 consecutive patients. In that report, the apex was the most frequent site (36%), and the overall PSM rate was 11.5%. In addition, 38.6% of PSM were in the apex, 34.6% were PL, 15.8% were MF, and 10.9% were in the BN. In the current study, the overall PSM rate was 25.1%, with 38.2% PL, 26.5% MF, 16.2% in the apex and 14.7% in the BN. Thus, the PL and MF sites were the most common PSM locations, not the apex. The apical surgical margin is usually reported to be the most common PSM site, but apical PSMs may result from factors other than cancer aggressiveness. Further, apical PSMs are thought to be affected by iatrogenic factors, such as surgical experience and maximizing urethral length. Outcomes associated with an increased rate of biochemical relapse have been reported. Our data from patients at high-risk showed a lower rate of PSM at the apex and a higher proportion of PL and MF PSMs than in the previous report. This result supports the conclusion that an apical margin may result from other factors and that tumor biology may be more important in patients at high-risk.

Several iatrogenic factors such as the type of procedure, technique, and surgeon volume and experience could influence PSMs in...
organ-confined tumors. In our study, the use of a single, experienced surgeon could eliminate these iatrogenic factors. A higher BMI can also increase the rate of iatrogenic PSMs in the apex. Coelho et al. suggested that intra-abdominal fat can obscure vision, working space, and instrumentation angles in the surgical field; thus, surgery may be suboptimal in patients with higher BMIs. Thus, they suggested that, in these technically difficult situations, the surgeon’s expertise is needed to prevent iatrogenic PSMs, especially in apical dissection. In our study, there was a higher rate of apical PSMs in T2 patients, which could be explained by BMI. Unfortunately, we could not perform subgroup analyses by PSM location due to an inadequate sample size. However, apical PSMs were more common in T2 patients, and patients with apical PSMs had higher BMIs in this study (data is not shown). In addition, BMI was an independent predictive factor of PSMs in multivariate analysis.

The most common location for PSMs in our study was PL, which is indicative of an aggressive cancer. Eastham et al. using retropubic RP data, suggested that the PSM at the PL site affect disease-free survival because the PL site has an abundance of neurovascular tissue that allows cancer cells to migrate more easily. In our study, the PL site was the most common location of PSMs, and the rate of apical PSM was lower than in our previous results. In addition, most PL and MF PSMs occurred in pT3 patients. Our results show that the PSM site in patients at high-risk is more affected by tumor aggressiveness than by iatrogenic causes. Although the role of PSM location is still controversial, the decision to add local therapy can be affected by the location and extent of the PSM. Many questions regarding PSM location remain, and an individualized approach and recommendation is still required. However, a thorough pathologic assessment of specimens is needed to create a treatment plan and decrease the risk of PSA relapse after RP.

Limitations of our study included the lack of enough patients for subgroup analysis by PSM location. In addition, we did not have a long enough follow-up to assess biochemical recurrence or cancer-specific mortality. The surgeries were performed by an experienced surgeon, so the PSM rate cannot be applied to low-volume centers. Another limitation of this study was the inability to report the exact number of high-risk patients who underwent salvage versus adjuvant external beam radiation therapy since most patients were referred from distant centers and continued their follow-up with their primary urologists. Finally, extended pelvic lymph node dissection (ePLND), removal of the common iliac, external iliac, internal iliac, and obturator lymph nodes, was not performed in these surgeries. However, ePLND is an essential part of surgical treatment and is recommended by the European Association of Urology guidelines for patients at high-risk. Therefore, RALP should be performed with ePLND to treat high-risk PCa, and further studies including ePLND should be performed.

CONCLUSIONS

The overall PSM rate in 271 patients at high-risk was 25.1%. This result shows that RALP is a promising surgical technique for treating high-risk PCa, but it should only be performed at experienced centers, and it should be compared with other techniques in randomized clinical trials to determine the best technique in terms of oncological outcomes. The pathological stage and percent of tumor in the surgical specimen were the only independent predictive factors of PSM, and preclinical variables cannot replace postoperative pathological outcomes in predicting PSMs. More large-scale RALP data are needed from patients at high-risk, and additional long-term studies should be performed to evaluate the effect of PSMs on biochemical recurrence and cancer-specific mortality.

AUTHOR CONTRIBUTIONS

SGK and OS participated in the design of the study and performed the statistical analysis. SGK, AMH and SS were involved in data collection and drafting the manuscript. KJP, JC, and VRP read and revised the manuscript critically for important intellectual content. VRP approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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