Predicting Factors for Biochemical Recurrence and Oncological Outcomes Following Laparoscopic Radical Prostatectomy in Rajavithi Hospital, Thailand

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Objective: To determine the predicting factor of biochemical recurrence and analysis of pathological and oncological outcomes following laparoscopic radical prostatectomy (LRP) at Rajavithi Hospital in Thailand
Material and Method: One hundred twenty men underwent laparoscopic radical prostatectomy between October 2006 and December 2011. Four men were excluded due to open surgical conversions and fourteen men were excluded due to lacking of follow-up. The remaining 102 men had a mean preoperative prostate specific antigen of 21.4 ng/ml (ranging from 0.4 to 185) and Gleason score of 6.2 (ranging from 6 to 10). Stage was cT1b in one case (1%), cT1c in 66 (64.7%), cT2 in 28 (27.5%), and cT3 in seven (6.9%). Immediate postoperative adjuvant therapy of twenty-six men was excluded from biochemical recurrence analysis.
Results: Mean follow-up period was 19.7 months (median 16, ranging from 2 to 54.8). Pathological stage was pT0N0 in two men (2%), pT2N0 in 78 (76.5%), pT3N0 in 11 (10.8%), and pT2-3N1 in 11 (10.8%). Positive surgical margin (SM) rates increased with higher stage (23.1% in pT2, 63.6% in pT3 and 81.8% in pT2-3N1, $p<0.0001$). Three-year biochemical recurrence-free survival was 87.1% for pT2N0 and 50% for pT3N0/N1 disease ($p = 0.025$), and 84.2% overall. Univariate analysis for age, preoperative PSA, postoperative Gleason score, pathological stage, and margin status showed that only margin status could be used as a predictor for biochemical recurrence.
Conclusion: Predicting factor for biochemical recurrence after LRP was positive SM status. From the oncological result, LRP in our experience is a safe and efficacious therapy for localized prostate cancer with acceptable and was consistent with results of previous studies.

Keywords: Prostate cancer, Laparoscopic radical prostatectomy, Biochemical recurrence

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Nowadays minimal invasive surgery is popular throughout the world. Laparoscopic radical prostatectomy (LRP) was pioneered in the 1990s[1-3] and became widespread in the 2000s. Initial studies described LRP technique, LRP perioperative outcomes, and short-term LRP complications[3-6]. Quality of life instruments were eventually applied to LRP and they demonstrated that continence, potency, and low positive margin rates were achievable[7-10]. Two approaches have been described for the laparoscopic procedure, transperitoneal and extra-peritoneal approach.

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Since the study by Guillonneau et al[11], several other European groups have added their data to the available literature on Biological Recurrence-Free Survival (BRFS) after LRP[12-15]. The more recent advent of robot assistance has greatly increased the application of laparoscopy to the treatment of clinically localized prostate cancer, such that robot assisted LRP is now offered at hundreds of centers throughout the United States. In Rajavithi Hospital, laparoscopic radical prostatectomy has been performed since 2006. Our technique was Montsouris technique laparoscopic radical prostatectomy[5]. Our technique used, perioperative and post-operative outcome have been previously presented by Thaidamrong et al[16]. The authors now report oncological outcomes and predicting factors for biochemical recurrence in patients who underwent LRP without robot assistance between 2006 and 2011.

Material and Method

Single surgeon (Danaiphand Akarasakul) performed 120 LRPs between October 2006 and December 2011. The LRP procedure was applied with the Montsouris technique. Four cases converted to open surgery were excluded from the analysis. Pelvic lymphadenectomy was performed in all patients with intermediate or high-risk disease (PSA greater than 10, Gleason greater than 6, stage greater than cT1c). Cavernous nerve preservation (nerve-sparing) was individualized but generally performed in men who declared themselves potent and who had less than clinical stage T2 disease and a predominance of Gleason pattern had less than 4 on biopsy samples from affected side.

Clinical and pathological staging was done using the 2002 AJCC TNM system and Gleason grading was assigned. The 14 men without any follow-up PSA data available were excluded from analysis. There remained 102 men in the authors' series and Table 1 lists their demographics and characteristics. Twenty-six patients who received immediate post-operative adjuvant treatment were excluded from biochemical recurrence-free survival analysis. Biochemical recurrence failure was defined and timed at the first postoperative PSA of 0.2 ng/ml or greater if a second confirmatory PSA was also 0.2 ng/ml or greater.

Pearson's Chi-square test was used to compare proportions among groups. BRFS was estimated using the Kaplan-Meier method and survival curves were compared using the log rank test. Univariate proportional hazards models were used to estimate the HR and 95% CI. The present study was approved by the research ethics committee of Rajavithi Hospital.

Table 1. Patient demographics

Characteristics	No. Pts (%)
Overall	102 (100)
Biopsy Gleason score	
6	68 (66.7)
7	16 (15.7)
8-10	18 (17.6)
Clinical stage	
cT1b	1 (1.0)
cT1c	66 (64.7)
cT2	28 (27.5)
cT3	7 (6.9)
Pathological stage	
pT0N0	2 (2.0)
pT2N0	78 (76.5)
pT3N0	11 (10.8)
pT2-3N1	11 (10.8)
Postop Gleason score	
4-6	58 (56.9)
7	26 (25.5)
8-10	18 (17.6)
Mean PSA (range)	21.4 (0.4-185)
Mean age ± SD	69.6±6.6

Results

Mean postoperative follow-up of 19.7 months (median 16, range 2 to 54.8), during which time there were 12 PSA recurrences. Overall, 3-year BRFS was 84.2%. As stratified by stage, 3-year BRFS was 87.1% in pT2N0 and 50% in pT3N0/N1 cases (p = 0.025, Fig. 1A). In addition to pathological stage, final Gleason score and surgical margin status were also associated with BRFS, that is 91.1% vs. 74.2% for final Gleason score less than 7 vs. 7 or greater and 93.5% vs. 42.9% for positive surgical margin status vs. negative surgical margin status (p = 0.018 and <0.0001, Fig. 1B, C). Preoperative PSA was not significantly associated with 3-year BRFS, although p = 0.187 (preoperative PSA <10 vs. PSA ≥10; 89.7% vs. 78.4%, Fig. 1D).

The positive surgical margin rate was 33% in total (Table 2). Positive surgical margin (SMs) were significantly increased at higher pathological stages, 23.1% in pT2, 63.6% in pT3 cases, and 81.8% in pT2-3N1 (p<0.0001).

Univariate proportional hazards modeling was done for preoperative PSA, patient's age, postoperative Gleason score, postoperative stage and SM status

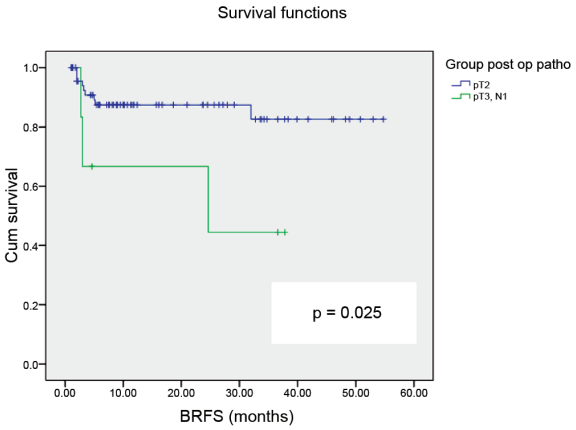

Fig. 1A BRFS after LRP by pathological stage.

(Table 3). Only SM status was predictor of BRFS on univariate analysis. Other factors were not significant predictors of BRFS.

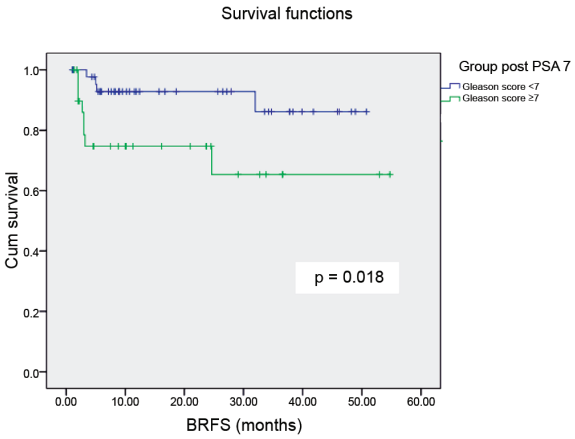

Fig. 1B BRFS after LRP by postoperative Gleason score.

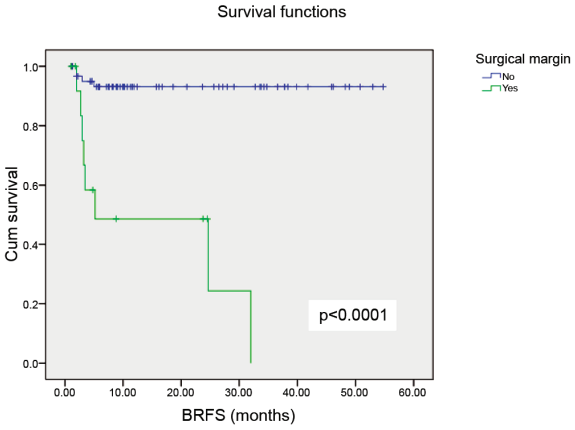

Fig. 1C BRFS after LRP by SM status.

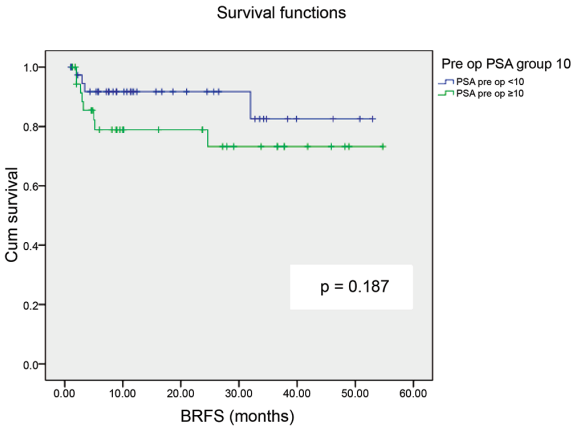

Fig. 1D BRFS after LRP by preoperative PSA.

Table 2. SM status by clinical and pathological stage

AJCC 2002 stage	Positive margin/total (%)
Clinical stage	
cT1c	17/66 (25.8)
cT2	10/28 (35.7)
cT3	7/7 (100)
Pathological stage	
pT2N0	18/78 (23.1)
pT3N0	7/11 (63.6)
pT2-3N1	9/11 (81.8)

Table 3. Univariate analysis proportional hazards models of predicting factor for biochemical recurrence following LRP

Variable	HR (95% CI)	p-value
PSA <10 vs. ≥10	0.93 (0.20, 4.26)	0.93
Age	1.03 (0.92, 1.15)	0.63
Postop GS <7 vs. ≥7	1.39 (0.09, 21.85)	0.82
Pathological stage: pT2N0 vs. pT3 and/or N1	1.06 (0.19, 6.02)	0.95
SM status (pos vs. neg)	9.91 (2.49, 39.43)	0.001

Discussion

The principle objective of radical prostatectomy is to completely excise the cancer. Important cancer control end points are pathologically organ-confined disease with clear surgical margins, biochemical recurrence (detectable serum PSA), local progression, metastases, cancer-specific survival, and overall survival. A rising serum PSA level (biochemical recurrence) is usually the earliest evidence of tumor recurrence after radical prostatectomy. The clinical spectrum of men with biochemical recurrence are 1) persistent or localized recurrence in prostatic bed, 2) a harbinger of detectable metastases, and 3) both local and systemic disease.

In the present study, LRP was performed in Rajavithi Hospital since 2006. The LRP procedure was variant of Montsouris technique[5]. The present study, single surgeon (Akarasakul D) was performed without robot assistance. The patient is placed in the steep Trendelenburg position. The first port was created at infraumbilical area by opened technique. The other port was created under laparoscopic vision. The extraperitoneal space was created by balloon dissector and port site was created after that. The authors started procedure by cleaning periprostatic fat and opening endopelvic fascia on both side. Dissection of bladder neck was performed by bladder neck preservation

technique. After the transection of bladder neck, the authors incised Denonvillier's fascia and identified vas deferens and seminal vesicles. Transection of vas deferens was performed and posterior aspect of prostate gland was approached. Apex of prostate gland was dissected. Dorsal venous complex was controlled and sutured. Prostatic apex and urethra were transected at level of verumontanum. Prostate gland was removed from prostatic fossa. Vesicourethral anastomosis was performed by Vicryl 2/0 curve 5/8 intracorporeal interrupted fashion. The authors inserted Foley catheter No.18 Fr before closing the last stitch. The prostate specimen was pushed in the bag and tube drain was inserted into the pelvis. The specimen was removed pass through infraumbilical port and closed abdomen at port site. Skin was closed by subcuticular stitches. There were 28 postoperative complications, which are urine leakage more than two weeks (11 cases), rectal injury (10 cases), hematoma (3 cases), lymphatic leakage more than two weeks (3 cases), and DVT (1 case). Perioperative result was reported by Thaidamrong[16] without long-term oncological outcomes. However, Oncological outcomes and predicting factor for biochemical recurrence was reported in this paper.

Positive SM is related to surgeon experience, extent of disease. In our study, positive SM is 33% in total. Positive SM increased significantly with higher stage (pT2 23.1%, pT3 63.6%). Localized disease (pT2) positive SM is comparable with international reports[11,15,17] except that the higher stage showed an inferior result to such reports as shown in Table 4.

According to our study, three-year BRFS was 84.2% in total (pT2N0 87.1%, pT3N0/N1 50%). That result was comparable with some previous reports[11-13,15] but showed inferior result to report from Pavlovich et al[18] as shown in Table 5.

Inferior result in positive SM and three-year BRFS from our study compared to study from Pavlovich et al[18]. This may be caused from significantly higher mean preoperative PSA (21.4 in our series vs. 6 in Pavlovich series) and postoperative Gleason grade in our series (Gleason 7 or greater in 43% vs. 25% in Pavlovich series). From Kaplan-Meier method pathological stage, final Gleason score and positive SM decreased survival significantly by statistics.

From univariate analysis, positive SM was only the strong predictor of biochemical recurrence. All surgeons, therefore, should be aware of positive surgical margin while performing LRP because of higher rate of recurrence.

Conclusion

Predicting factor for biochemical recurrence after LRP was positive SM status. From oncological result, LRP in our experience is a safe and efficacious therapy for localized prostate cancer with acceptable and compared well with previous studies. It can

Table 4. Positive SM reports in the previous published series

Guillonneau et al. (2003)[11], n = 1,000	Positive SM was 6.9%, 18.6%, 30% and 34% for pT2a, pT2b, pT3a and pT3b.
Salomon et al. (2002)[15], n = 200	Positive SM for pT2 was 22%.
Tse E et al. (2004)[17], n = 200	Positive SM was 0% for pT2a, 20% for pT2b, 52% for pT3a and 53% for pT3b. Overall positive SM was 27%.
Pavlovich et al. (2008)[18], n = 508	Positive SM was 8.2% for pT2 and 39.3% for pT3. (mean preoperative PSA was 6, postoperative Gleason 7 or greater was 25%)
Present series, n = 102	Positive SM was 23.1% for pT2, 63.6% for pT3. Overall positive SM was 33%.

Table 5. 3 year BRFS reports in previous published series

Guillonneau et al. (2003)[11], n = 1,000	3 yr BRFS was 91.8% for pT2aN0, 88% for pT2bN0, 77% for pT3aN0, 44% for pT3bN0 and 50% for pT1-3N1.
Lein M et al. (2006)[12], n = 1,000	3 yr BRFS was 90% for pT2, 80.3% for pT3a, and 72.4% for pT3b.
Rassweiler et al. (2005)[13], n = 500	Overall 3 yr BRFS was 83%.
Salomon et al. (2002)[15], n = 200	Overall 3 yr BRFS was 84%.
Pavlovich et al. (2008)[18], n = 508	3 yr BRFS was 98.2% for pT2N0, 78.7% for pT3N0/N1 and 94.5% overall. (mean preoperative PSA was 6, postoperative Gleason 7 or greater was 25%)
Present series, n = 102	3 yr BRFS was 87.1% for pT2N0, 50% for pT3N0/N1 and 84.2% overall.

result in excellent BRFS outcomes in patients with pathologically organ confined disease.

Potential conflicts of interest

None.

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ปัจจัยเสี่ยงในการเกิด biochemical recurrence และ oncological outcome หลังการผ่าตัดมะเร็งต่อมลูกหมากด้วยวิธี laparoscopic radical prostatectomy ในโรงพยาบาลราชวิถี

ศรายุทธ วิริยะศิริพงศ์, ดนัยพันธ์ อัครสกุล, ธเนศ ไทยดำรงค์, สมจิตร์ ดวงแข

วัตถุประสงค์: เพื่อศึกษาปัจจัยเสี่ยงในการเกิด biochemical recurrence และวิเคราะห์ผลการรักษาทางมะเร็งวิทยา และพยาธิวิทยา หลังการผ่าตัดมะเร็งต่อมลูกหมากด้วยวิธี laparoscopic radical prostatectomy ในโรงพยาบาลราชวิถี

วัสดุและวิธีการ: การศึกษาทำในผู้ป่วย 120 ราย ที่ได้รับการผ่าตัด laparoscopic radical prostatectomy ในโรงพยาบาลราชวิถีระหว่าง เดือนตุลาคม พ.ศ. 2549 ถึงเดือนธันวาคม พ.ศ. 2554 โดยคัดออกจากการศึกษา 4 ราย เนื่องจากต้องเปลี่ยนการผ่าตัดเป็นวิธี open และคัดออก 14 ราย ที่ไม่มาติดตามการรักษาต่อ ผู้ป่วยที่เหลือ 102 ราย มีค่าเฉลี่ย PSA 21.4 (0.4-185) และ Gleason score 6.2 (6-10) มี stage cT1b 1 ราย (1%), cT1c 66 ราย (64.7%), cT2 28 ราย (27.5%), cT3 7 ราย (6.9%) ผู้ป่วย 26 ราย ที่ได้รับ adjuvant therapy ทันทีหลังการผ่าตัดจะถูกคัดออกจากการศึกษา biochemical recurrence

ผลการศึกษา: ระยะเวลาเฉลี่ยในการติดตามการรักษาคือ 19.7 เดือน มี pathological stage pT0N0 2 ราย (2%), pT2N0 78 ราย (76.5%), pT3N0 11 ราย (10.8%) และ pT2-3N1 11 ราย (10.8%) อัตราการเกิด positive surgical margin จะสูงขึ้นใน stage ที่สูงขึ้น (23.1% ใน pT2, 63.6% ใน pT3 และ 81.8% ใน pT2-3N1, $p<0.001$) อัตราการเกิด 3-year biochemical recurrence-free survival คือ 87.1% ใน pT2N0, 50% ใน pT3N0/N1 และ 84.2% ในทั้งหมดการวิเคราะห์ univariate analysis สำหรับอายุ, ค่า PSA ก่อนผ่าตัด, Gleason score หลังผ่าตัด, pathological stage และ margin status จากการศึกษาพบว่า margin status เท่านั้นที่เป็นปัจจัยเสี่ยงในการเกิด biochemical recurrence

สรุป: ปัจจัยเสี่ยงในการเกิด biochemical recurrence หลังการผ่าตัด laparoscopic radical prostatectomy คือ positive surgical margin และผลการศึกษาทางมะเร็งวิทยาพบว่าการผ่าตัด laparoscopic radical prostatectomy ในโรงพยาบาลราชวิถีมีความปลอดภัย และมีประสิทธิภาพเทียบเท่าการศึกษาอื่นในการผ่าตัดมะเร็งต่อมลูกหมากระยะ localized