ORIGINAL ARTICLE

MEDIUM TO LONG TERM OUTCOME OF PATIENTS TREATED WITH RADICAL RETROPUBIC PROSTATECTOMY FOR CLINICALLY LOCALIZED PROSTATE CANCER

Syed Muhammad Nazim, Mehwash Nadeem, Nuzhat Farooqui, Farhat Abbas
Section of Urology, Department of Surgery, The Aga Khan University Hospital, Karachi-Pakistan

Background: To evaluate the medium to long term cancer control, morbidity, mortality and functional outcome in men undergoing open radical retro pubic prostatectomy (RP) and pelvic lymph node dissection (PLND) for clinically localized adenocarcinoma prostate (CaP). **Methods:** A total of 200 patients were operated with intention to treat for localized CaP, from January 1998 to October 2013. Patients' characteristics, operative data, progression-free survival rate, recurrence rate, morbidity, mortality and functional outcome were analysed. Statistical analysis was performed using SPSS v.19. Kaplan Meir curves were plotted for survival estimate. **Results:** The mean age was 63.6±6.2 years and median pre-operative PSA was 11±2.1 ng/ml. RP and bilateral PLND were performed in 172 patients of which 35 (20%) had nerve-sparing surgery. In 8 cases with gross lymph node metastasis at frozen section, only bilateral orchiectomy was done while remaining 20 patients had RRP+PLND with bilateral orchiectomy. The final study population was therefore 192. Mean length of hospital stay was 6±1 day with zero 30-day perioperative mortality. On final histopathology, 78% of tumours were confined to the prostate gland. Twenty four (12.5%) patients had positive surgical margins. Overall, 163 (85%) patients regained full continence. Nearly half of patients with nerve sparing approach were potent without any supportive measures. Most common long term complication was urethral stricture (8%). At median follow up of 41 months, the progression-free and overall survival rates were 85% and 94%, respectively. Seven percent had biochemical recurrence while 4% had local recurrence and 4% had metastatic disease. **Conclusions:** Our results indicate that RP has an excellent potential for cancer control with low morbidity and good functional outcome in men with localized CaP. Our data is consistent with larger series from other centres across the globe.

Keywords: Prostate Cancer; Radical Prostatectomy; Long term outcome
J Ayub Med Coll Abbottabad 2016;28(4):653–9

INTRODUCTION

Prostate cancer is one of the commonest cancers and a leading cause of death in western world.[1] Organ confined or localized disease offers the best chance of cure.[2] Treatment options for this category include radical prostatectomy (RP), active surveillance, external beam radiation therapy (EBRT) or brachytherapy, or hormonal therapy (HT)[2]. Till now, no open label study has directly compared the treatment arms and due to lack of randomized studies, the best treatment for organ confined prostate cancer is based upon information from historic series.[3,4]

RP is known to be most effective and standard of care treatment for organ confined prostate cancer.[5] First described over a century ago, with the advancement in diagnostic and surgical techniques, it has become the commonest treatment for prostate cancer with excellent long term survival outcomes.[5,6] The objective of open RP is to achieve complete excision of prostate in order to provide not only optimal cancer control but to maintain urinary continence and sexual potency by preserving the integrity of anatomic structures, thus maintaining quality of life.[5]

We report the first study from Pakistan describing the outcome of open radical retro-pubic prostatectomy (RP) for clinically localized adenocarcinoma prostate.

MATERIAL AND METHODS

This study is an analysis of the hospital record of more than 15 years from Jan 1998 to October 2013. Patients with clinically localized prostate cancer who underwent bilateral pelvic lymph node dissection (PLND) with intent to treat by RP with at least one year follow up at The Aga Khan University and Hospital were included. Their clinical and pathological data were reviewed and analysed. Patients who had incomplete data, biopsies done outside our hospital, those who had previous radiation or neo-adjuvant hormonal treatment and had histopathology other than adeno-carcinoma were excluded. Pre-operative data included serum prostate specific antigen (PSA), clinical staging done by digital rectal examination & axial imaging (CT scan/ MRI pelvis)±Bone scan. Trans rectal ultrasound

(TRUS) guided systemic biopsy of prostate (minimal six cores) was done in all patients and using Gleason scoring, prostate cancer was graded histologically. The operative and follow up data was reviewed from the notes.

The procedure was performed under general anaesthesia with lower midline incision. At first, modified obturator lymph node dissection was done and sent for frozen section analysis. If frozen section was negative, standard radical retro-pubic prostatectomy was performed. Unilateral/Bilateral preservation of neurovascular bundles were done where indicated. A water tight urethro-vesical anastomosis was subsequently performed over a 20 French three way Foley's catheter which was removed after 10–14 days.

Patients were seen in clinic at 2 weeks, 6 weeks and then quarterly for first 2 years and then every 6 monthly. During each post-operative visit, a focused history was taken and examination was performed. Serum PSA levels were checked quarterly for the initial 2 years and then every 6 monthly.

The oncological outcome parameters assessed were overall survival (OS), cancer specific survival (CSS) and Progression free survival (PFS). Biochemical recurrence (BCR) was defined as a PSA level of >0.2 ng/mL and PFS as no evidence of disease progression in terms of rise of PSA, local recurrence or metastasis. The short and long term complications and functional outcome in terms of continence and potency status were also reviewed. Urinary continence was defined as no need to wear any protective pads and sexual potency as achieving and maintaining penile erections sufficient for vaginal intercourse with or without oral therapy.

The statistical analysis was performed on SPSS V. 19. All statistical tests were 2 sided and a *p*-value of <0.05 was considered to be significant. Kaplan Meier tests were applied for survival estimates and their comparison was made using log-rank test. Uni and multivariate cox regression analyses were done to evaluate relationship between overall and progression free survival with important clinico-pathological parameters.

RESULTS

A total of 200 patients were operated with intent of RP during the study period. RP and bilateral PLND were performed in 172 patients of whom nerve-sparing surgery was done in 35 cases (20%). Gross lymph node metastasis was found in 8 cases and hence only bilateral orchiectomy was done (and therefore excluded from the study) while remaining 20 patients had RP+PLND with bilateral orchiectomy. The final study population was therefore 192. The mean age was 63.6±6 years (range: 43–77 years). The initial presentation were lower urinary tract obstructive symptoms (71%); followed by elevated level of PSA in 25%, gross haematuria and incidental diagnosis at transurethral resection of prostate (2% each).

The patient and disease characteristics are shown in table-1. Median pre-operative PSA was 11±2.1 ng/ml. Thirteen percent of patients had high grade disease with Gleason score ≥8. Nearly ¾ th of our patients had palpable clinical disease and 31% of our patients belonged to high risk category according to D'Amico's classification.

Table-2 shows the peri-operative outcome. The Mean operating time was 240±44 minutes. Nerve sparing surgery was performed in 35 patients with 25 patients had bilateral and 10 had unilateral preservation. The mean length of hospital stay was 6±1 day.

There was no 30-days peri-operative mortality. Three patients developed anastomotic leakage managed conservatively with prolonged placement of indwelling catheter and drain. One patient had intra-operative rectal injury which was recognized and managed on operating table with 2-layered closure. Four patients had inadvertent dislodgement of catheter which was replaced under cystoscopic guidance under local anaesthesia. Most common long term complication was urethral stricture (8%) followed by bladder neck contracture (3%).

On final histo-pathology 78% of tumours were confined to prostate, seminal vesicle invasion was seen in 13% and nodal metastasis was found in 9%. Positive surgical margins were found in 24 (12.5%) of patients, out of which 13 patients required adjuvant treatment with radiation or hormonal therapy subsequently due to rising PSA levels, while remaining had no evidence of disease recurrence on long term follow up. Overall, 85% of the patients were fully continent with mean time of return of continence being 5±4 weeks. Mild to moderate stress urinary incontinence was found in 15% of patients.

Among 35 patients who had nerve sparing RP, 16 (47%) were potent without any supportive measures, while rest of patients required oral medication (PDE5 inhibitors). Patients in bilateral nerve preservation group had early return of potency in comparison to the unilateral nerve preservation group.

At median follow up of 41 months, a total of 14 (7%) patients died, mostly due to reasons unrelated to prostate cancer (5%). The 5-year and 10-year overall survival (OS) are 92% and 58% respectively (Figure-1). On univariate analysis, amongst all clinico-pathological factors, only age was

found to be statistically significant (p<0.05). Pre-operative PSA (p=0.06), Gleason scoring (p=0.06), Pathological stage (p=0.41), nodal status (p=0.51), and disease progression (p=0.06) were not found to be statistically significant factors for overall survival. The 5-year and 10-year cancer specific survival (CSS) rates were 98% and 80%, respectively.

A total of 21 patients had disease progression during follow up. The progression free survival (PFS) rate at 5 and 10 years were 85% and 68% respectively. Figure 2 shows PFS status using Kaplan Meier curves amongst important subgroups based on final pathology, i.e., surgical margin status, nodal status, organ confined or not. Serum PSA (p=0.03), Gleason score (p=0.02), clinical stage (p=0.03), the D'Amico risk group (p=0.02), margin positivity (p=0.001) and final histopathology stage (p<0.001) were the important predicting factors affecting the PFS on univariate and multivariate analyses (Table-3).

A statistically significant difference (p<0.01) in PFS was also observed among patients who had RRP+PLND compared with patients who had RRP+PLND+bilateral orchidectomy (Figure-3).

Table-1: Patients and Tumour characteristics (n=192)

Age at diagnosis (Mean±SD)	**63±6.2 (43–77)**
ASA grade (%)	
I	54 (28)
II	102 (53%)
III	36 (19%)
PSA at diagnosis (ng/ml) (Median±SD)	11±2.1 (1–121)
PSA level (ng/ml) (%)	
<4	21 (11%)
4 to <10	63 (33%)
10–20	54 (28%)
>20	54 (28%)
Pre-op Biopsy Gleason score (%)	
≤6	96 (50%)
7	71 (37%)
≥8	25 (13%)
Clinical stage (%)	
cT1NoMo	52(27%)
T1a-T1b	4 (2%)
T1c	48(25%)
cT2NoMo	138 (72%)
T2a	63 (33%)
T2b	31 (16%)
T2c	44(23%)
cT3NoMo	2 (1%)
D'Amico Risk groups	
Low	81 (42%)
Intermediate	51 (26%)
High	60 (31%)

Table-2: Peri-operative outcomes (n =192 RRP group)

Operative time (min) Mean±SD	240±44 (150–370)
Blood loss (mls) Mean±SD	970±475 (300–2800)
Blood transfusions (units) Mean±SD	1 (0–5)
Length of hospital stay (days) Mean±SD	6±1 (3–12)
Nerve sparing procedures (%)	35 (18%)
Bilateral	25 (13%)
Unilateral	10 (5%)

Table-3: Uni-variate and multivariate logistic regression analysis of variables' association with progression free survival (PFS) in Radical Prostatectomy

Variables	**n**	**Uni-variate analysis**	**Multivariate analysis OR (95% CI)**	
			Lower Bound	**Upper Bound**
Age			--	--
<60	55			
≥60	137	0.12		
p-value				
PSA			--	--
Up to 10	83			
10.1–20	52	**0.036**		
>20	57			
p-value			**0.029**	
Gleason Score			.662	3.837
6	112			
7	33	**0.024**		
8–10	47			
p-value			**0.020**	
Clinical Stage			.413	1.971
cT1a-cT2b	104			
cT2c	31	**0.003**		
cT3 and above	57			
p-value			**0.020**	
Risk Group			.136	1.046
Low	65			
Intermediate	34	**0.002**		
High	93			
p-value			**0.02**	
Nodal Status			--	--
Positive	163			
Negative	29	**0.083**		
***p*-value**			0.379	
Margin Status			1.520	24.11
Positive	45	**0.001**		
Negative	147			
p-value			**0.011**	
Seminal Vesicle Involvement			.550	14.98
Present	39	**0.04**		
Absent	153			
***p*-value**			**0.030**	
Pathological Stage			.368	11.00
Organ Confined	111	**0.03**		
Locally Advance	81			
***p*-value**			**0.03**	

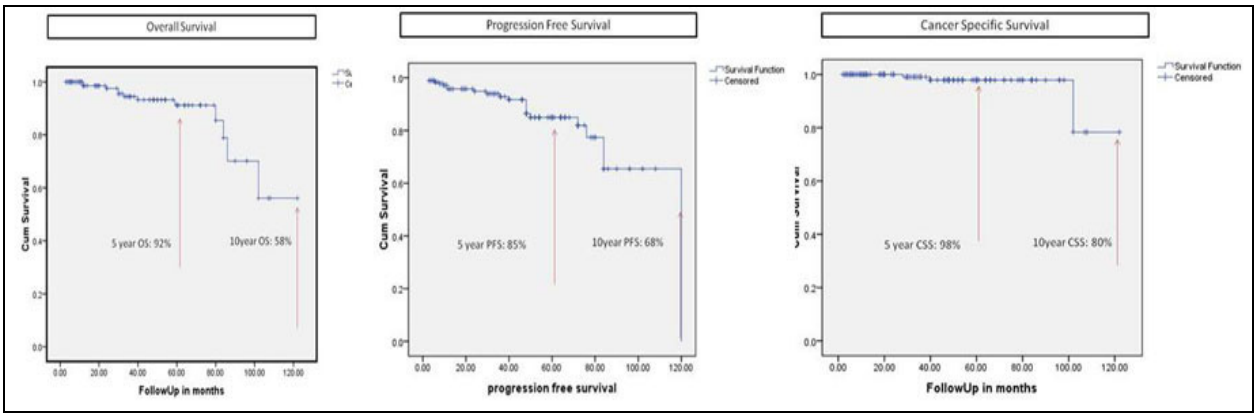

Figure-1: Kaplan Meier analysis of overall survival (OS), Progression free survival (PFS) and Cancer specific survival (CSS) for patients who underwent open radical retro pubic prostatectomy

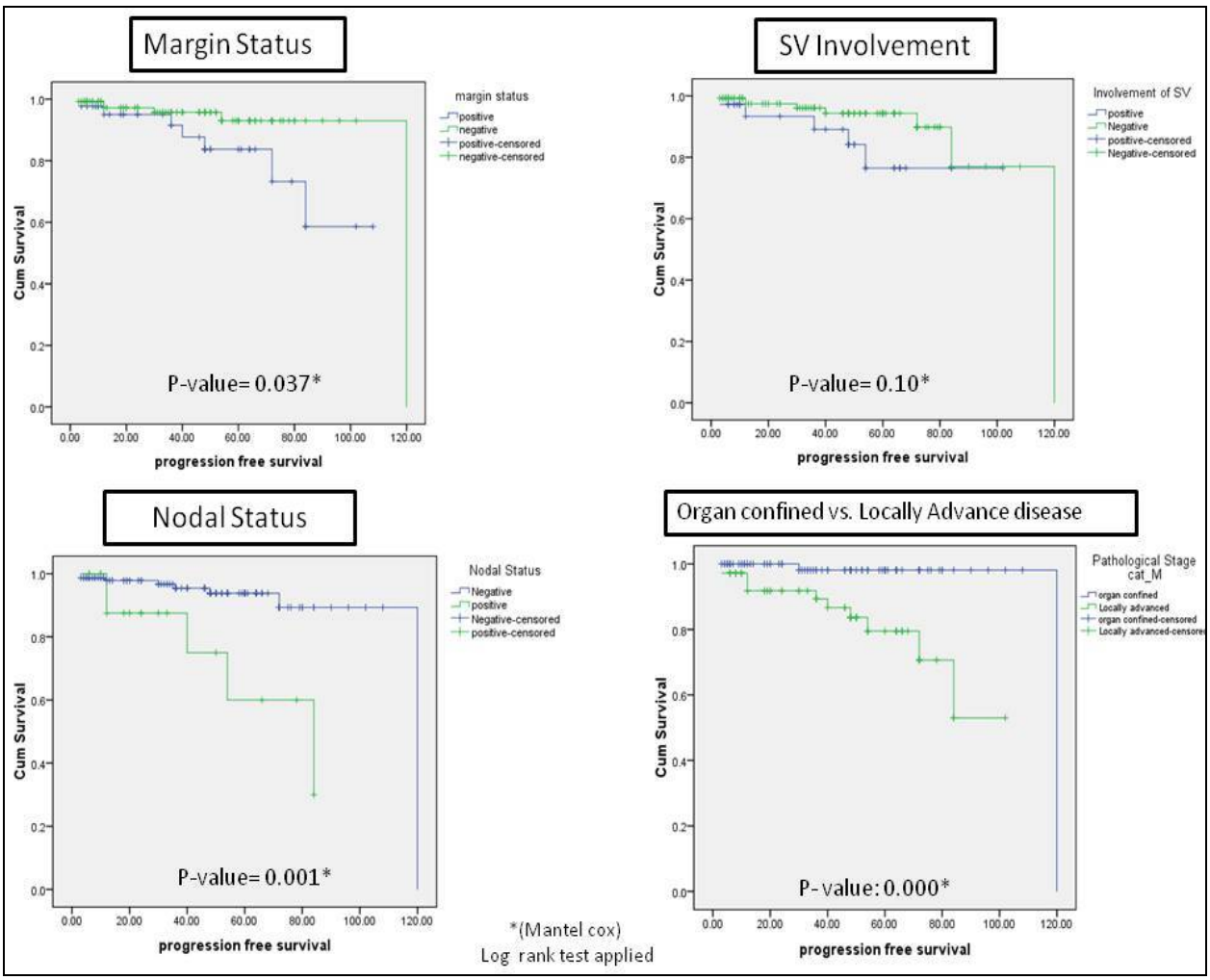

Figure-2: Comparisons of Kaplan Meier analysis of Progression free survival (PFS) for Margin status, seminal vesicle involvement, nodal status and disease extension (organ confined vs. locally advanced disease) in patients who underwent open retro pubic radical prostatectomy.

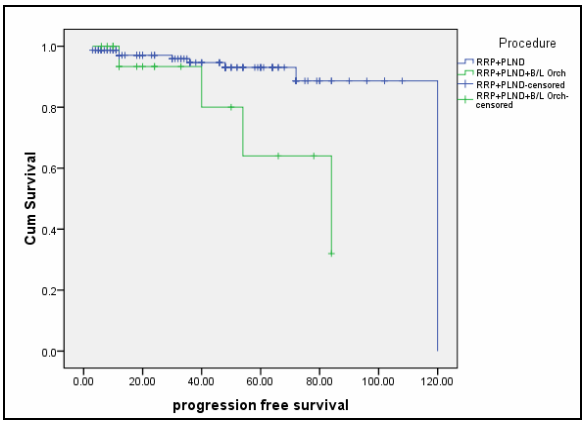

Figure-3: Comparisons of Kaplan Meier analysis of Progression free survival (PFS) among patients who underwent RRP + PLND vs. RRP + PLND+ Bilateral orchiectomy

DISCUSSION

Prostate cancer is the most common non-cutaneous malignancy in developed world.[1] The epidemiology of this disease is not correctly known in Pakistan due to lack of national level cancer registry. Moreover, because of cultural, geographical and economic diversity of this region, the treatment of prostate cancer in Asia is variable and non-standardized.[7]

Since its introduction in 1980's, radical prostatectomy has passed the test of time and is recommended as a treatment for organ confined prostate cancer patients with a life expectancy of >10 years.[5] In the era of PSA screening, more and more patients are being diagnosed with low-grade, low-stage disease leading to disease free survival rates approaching 90% at 5 years after RP.[6] RP has shown longer and durable results as compared to other treatment options in terms of cancer specific survival and it also offers a better assessment of the true pathological status of the disease.

Besides clinico-pathological variables such as PSA, histological features (i.e., Gleason grade, presence or absence of extra prostatic extension, surgical margin status, seminal vesicle and lymph node involvement) the peri-operative, oncological and functional outcome following radical prostatectomy also depends on the surgeons' experience and technique.[8]

Most of patients in our series (73%) presented symptomatically and only a quarter had cancer detection through PSA screening. Various prognostic tools and nomograms are available that can pre-operatively predict the pathological and oncological outcome following radical prostatectomy. We used Partin's tables for our patients and previously have found it to have a high predictive value in Pakistani patients.[9]

Compared to our initial report of 23 patients who underwent RP[10] the peri-operative parameters such as mean operative time, blood loss, need for transfusion, hospital stay and functional outcomes have improved over years.

According to D'Amico criteria, the characteristics of high risk prostate cancer are PSA of >20 ng/ml, Biopsy Gleason score of >8 or clinical stage $\geq$T2C.[3] Thirty one percent of our patients belonged to high risk D'Amico's group with increased mean PSA, advanced disease and delayed presentation. However, the overall, cancer specific and biochemical recurrence free survival are comparable to the larger series. The reported 10-year PSA progression free survival (PFS) rate in literature is approximately 85% in patients with organ confined disease which reduces to approximately 55% among those with a positive surgical margin (PSM).[11] Those patients who have pathologically proven non-organ confined disease are at increased risk of rapid disease progression with a reported biochemical recurrence (BCR) and cancer specific survival (CSS) of 40% and 63–90 % respectively.[12] Our study showed a 68 % progression free survival (PFS) and 80% cancer specific survival (CSS) with no evidence of local recurrence or metastasis at 10 years respectively.

A positive surgical margin (PSM), i.e., detection of cancer at the edge of resected specimen is a quality indicator of RP and is an independent predictor for biochemical recurrence (BCR) and prostate cancer specific mortality.[13] During open RP, tactile feedback permits intraoperative decision making to reduce positive surgical margin and thus improving cancer control compared to minimally invasive radical prostatectomy techniques.[14] Depending upon clinical and pathological factors, large series of open prostatectomy have reported overall positive surgical margin rates between 8% and 35%.[13,15] Swindle *et al* reported an overall PSM of 12.9% in their series of 1389 consecutive patients who underwent open RP for clinical stage T1-T3 disease. PSM was 6.8% in patients with pT2 increasing up to 23% in patients with pT3 disease.[15] The positive surgical margin rate in our study was 12.5%. This compares well with larger western series given that only 25% of our patients had clinically T1c disease and majority had clinically palpable (i.e., T2 & T3) disease. We did not use neo-adjuvant treatment in our cases. In literature, it is widely accepted that neo-adjuvant treatment can affect the rate of positive surgical margin.

Preservation of potency is an important measure for quality of life in patients undergoing RP. Besides the pathological factors, surgeon's experience, nerve sparing technique and appropriate patient selection is a key factor to achieve this

outcome.[5,16] The reported potency rates are ranging between 56–68% in large series following nerve sparing RP.[5,16] We performed nerve sparing surgery in a select group of patients, i.e., younger age with preserved potency status prior to surgery and non-palpable disease. Nearly half of our patients with nerve sparing procedure are potent without the need for any supportive measures. We did not use any objective tool or validated questionnaire like IIEF for grading the severity of erectile dysfunction.

We defined urinary continence as no need for any protective pads. The mean time for return of continence was 5 weeks and overall 85% of our patients were totally continent. A number of patients though may experience occasional leak of a few drops of urine but not on a regular basis. In literature, the reported continence rates at 3 months with zero pad requirements vary greatly with continence rates ranging between 17–76%.[17,18] This wide discrepancy b/w continence rate is not only due to difference in socio-demographic and clinical factors but because of the difference and heterogeneity of methodology for assessing continence.[17] A lower continence rate is reported from trials using validated questionnaire for its evaluation rather than ones which rely on physicians' assessment only.[17,18]

Minimally invasive prostatectomy, i.e., laparoscopic (LRP) and Robot assisted laparoscopic prostatectomy (RALP) have developed in last few years with approximately 67% of procedures being performed robotically in 2009 in United States.[19] Comparison of the oncological outcomes such as biochemical recurrence, survival statistics and functional outcomes like continence and potency is still controversial as most of these are single institution series with heterogeneous population of patients from different centres. A randomized control study of robot assisted laparoscopic RP (RALP) versus open RP is currently enrolling the patients and would compare the long term oncological outcome.[20]

The clinical advantages of minimally invasive radical prostatectomy are reduced blood loss, shorter hospital stay and lower analgesia requirements.[19] With the development and advancement of laparoscopic surgery and commissioning of robotic surgery in Pakistan, these advantages could be translated to the given patient population, provided there is clear evidence as being sought globally.

To our knowledge, this is the first study form Pakistan about the medium to long term outcome of open RP. Our data confirms the excellent cancer control potential of radical prostatectomy with good functional outcomes however, the effective management of prostate cancer in a third world country like Pakistan is far from acceptable as majority of patients still present with advanced and metastatic disease which cannot be managed with curative intent. Open radical prostatectomy is probably the most cost effective treatment for organ confined prostate cancer and therefore, in Pakistan, strategies should be devised for the early detection of prostate cancer and patients' access to this procedure should be increased. Moreover, strategies should also be devised to increase the number of surgeons with training and expertise in this surgery.

CONCLUSIONS

Our results indicate that RP has an excellent potential for cancer control with low morbidity and good functional outcome in men with localized CaP. Our data is consistent with larger series from other centre across the globe.

AUTHORS' CONTRIBUTION

SMN: Study design, data collection, literature search, manuscript writing, and proof reading. MN: Study design, data collection & analysis. NF: Data collection and analysis. FA: Conception, study design and overall supervision.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64(1):9–29.
2. Kupelian PA, Elshaikh M, Reddy CA, Zippe C, Klein EA. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. J Clin Oncol 2002;20(16):3376–85.
3. D'Amico AV, Whittington R, Malkowicz SB, Cote K, Loffredo M, Schultz D, *et al*. Biochemical outcome after radical prostatectomy or external beam radiation therapy for patients with clinically localized prostate carcinoma in the prostate specific antigen era. Cancer 2002;95(2):281–6.
4. González-San Segundo C, Herranz-Amo F, Alvarez-González A, Cuesta-Álvaro P, Gómez-Espi M, Paños-Fagundo E, *et al*. Radical prostatectomy versus external-beam radiotherapy for localized prostate cancer: long-term effect on biochemical control-in search of the optimal treatment. Ann Surg Oncol 2011;18(10):2980–7.
5. Walsh PC. Radical prostatectomy for localized prostate cancer provides durable cancer control with excellent quality of life: a structured debate. J Urol 2000;163(6):1802–7.
6. Sriprasad S, Feneley MR, Thompson PM. History of prostate cancer treatment. Surg Oncol 2009;18(3):185–91.
7. Williams S, Chiong E, Lojanapiwat B, Umbas R, Akaza H. Management of prostate cancer in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013. Lancet Oncol 2013;14(12):e524–34.
8. Alemozaffar M, Sanda M, Yecies D, Mucci LA, Stampfer MJ, Kenfield SA. Benchmarks for Operative Outcomes of Robotic and Open Radical Prostatectomy: Results from the Health Professionals Follow-up Study. Eur Urol 2015;67(3):432–8.
9. Nazim SM, Abbas F, Islam M, Ahmad Z. Validation of Updated Partin's Table in Pakistani Patients undergoing Radical Prostatectomy for Prostate Cancer. J Cancer Sci Ther 2011.
10. Abbas F, Siddiqui K, Biyabani SR, Hasan SH, Talati J. Early Surgical Results with intent to treat by Radical Retropubic

Prostatectomy for Clinically localized Prostate Cancer. J Pak Med Assoc 2002;52(5):200–5.
11. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol 2004;172(3):910–4.
12. Loeb S, Smith ND, Roehl KA, Catalona WJ. Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer. Urology 2007;69(6):1170–5.
13. Wright JL, Dalkin BL, True LD, Ellis WJ, Stanford JL, Lange PH, *et al*. Positive surgical margins at radical prostatectomy predict prostate cancer specific mortality. J Urol 2010;183(6):2213–8.
14. Hubanks JM, Umbreit EC, Karnes RJ, Myers RP. Open radical retropubic prostatectomy using high anterior release of the levator fascia and constant haptic feedback in bilateral neurovascular bundle preservation plus early postoperative phosphodiesterase type 5 inhibition: a contemporary series. Eur Urol 2012;61(5):878–84.
15. Swindle P, Eastham JA, Ohori M, Kattan MW, Wheeler T, Maru N, *et al*. Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol 2008;179(5 Suppl):S47–51.
16. Ayyathurai R, Manoharan M, Nieder AM, Kava B, Soloway MS. Factors affecting erectile function after radical retropubic prostatectomy: results from 1620 consecutive patients. BJU Int 2008;101(7):833–6.
17. Herrmann TR, Rabenalt R, Stolzenburg JU, Liatsikos EN, Imkamp F, Tezval H, *et al*. Oncological and functional results of open, robot-assisted and laparoscopic radical prostatectomy: does surgical approach and surgical experience matter? World J Urol 2007;25(2):149–60.
18. Lepor H, Kaci L. The impact of open radical retropubic prostatectomy on continence and lower urinary tract symptoms: a prospective assessment using validated self-administered outcome instruments. J Urol 2004;171(3):1216–9.
19. Stitzenberg KB, Wong YN, Nielsen ME, Egleston BL, Uzzo RG. Trends in radical prostatectomy: centralization, robotics, and access to urologic cancer care. Cancer 2012;118(1):54–62.
20. Gardiner RA, Yaxley J, Coughlin G, Dunglison N, Occhipinti S, Younie S, *et al*. A randomised trial of robotic and open prostatectomy in men with localised prostate cancer. BMC Cancer 2012;12:189.

Received: 13 January, 2016	*Revised:4 June, 2016*	*Accepted: 30 October, 2016*

Address for Correspondence:

Syed Muhammad Nazim, Section of Urology, Department of Surgery, The Aga Khan University Hospital, Karachi-Pakistan
Cell: +92 300 223 3722
Email: muhammad.nazim@aku.edu