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Early Surgical Results with intent to treat by Radical Retropubic Prostatectomy for Clinically localized Prostate Cancer

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Abstract

Aims: To evaluate the early cancer control rates, morbidity and mortality in men undergoing radical retropubic prostatectomy (RRP) for clinically localized adenocarcinoma prostate.

Methods: Patient's characteristics, operative data, progressive-free survival rates, morbidity and mortality were analyzed for 23 men with clinical T1-2 prostate cancer who underwent surgery with an intent to treat by RRP between December 1997 to July 2001.

Results: Patient's mean age was 63 ± 6.2 years (range 51 to 76 years) with American Society of Anesthesiology (ASA) status I in 4%, II in 65% and III in 31%. Two third of the patients had lower urinary tract obstructive symptoms, followed by hematuria (9%) and back pain (4%). Clinical stages were Tib in 4%, Tic in 9%, T2a in 17%, T2b in 22% and T2c in 48% of the patients. Mean pre-operative serum prostate specific antigen (PSA) was 25 ± 29 ng/ml (1.110 99.3). Bilateral pelvic lymphnode dissection (PLND) and RRP was performed in 20 cases (nerve-sparing RRP 5 cases). In 3 cases with gross lymph node metastasis at frozen section, only bilateral orchidectomy was done. The mean operative time was 270 ± 65 minutes and mean blood loss was 1097 ± 654 mls. Packed cell transfusions were nil in 26%, 1-2 units in 44%, 3-4 units in 26% and 5 units in 4% of the patients who underwent RRP. The mean length of hospital stay was 10.2 ± 1 days. Out of 20 patients who underwent RRP, 65% of tumors were confined to the specimen, 20% had seminal vesicle invasion and 15% had nodal metastasis. There was no pen-operative mortality while 2 patients developed epididymo-orchitis and 1 had myocardial ischemia (without infarction). Overall 87% of the patients were fully continent and 13% had mild to moderate stress urinary incontinence. The mean time of return of continence was 11.5 ± 11.6 weeks. Two of the 3 patients (66%) with follow up information and having undergone nerve-sparing RRP are potent.

At a mean follow up of 19.4 ± 13 months (range 3-45 months), 20 of 23 total patients (87%) and 17 of 20 RRP patients (85%) remained free of disease recurrence with PSA 0.4 ng/ml.

Conclusion: Our early results confirm the excellent potential for cancer control and low morbidity of radical prostatectomy for men with localized prostate cancer. These results are in conformity with the vast Western experience. Long-term results will be provided (JPMA 52:200; 2002).

Introduction

Three to four decades ago, prostate cancer ranked low as a cause of morbidity and mortality for the Western males¹⁻³. Today, it represents the most commonly diagnosed related death⁴. It is estimated that during the year 2001, it would account for 31% of newly diagnosed cancers

and 11% of cancer-related deaths in American men⁴.

This dramatic increase in the disease burden has been attributed to availability of refined methods of diagnosis (regular digital rectal examination, prostate specific antigen blood test, transrectal ultrasound, systematic prostatic biopsy), increased life expectancy with an ever aging population, as well as, to enhanced awareness about the disease in Western community^{5,6}.

The disease burden however, remains remarkably different between the Eastern and the Western countries⁷. The age-adjusted prostate cancer mortality rates from China, Japan and other Eastern countries appears less threatening than those reported from Europe and USA⁴. While the exact reasons remain unclear, genetic, environmental and dietary factors have been implicated⁸. Interestingly despite widely variable incidence of clinically detectable cases between different populations, autopsy studies from around the world show no variation in the prevalence of small latent cancers in men who die with no clinical evidence of prostate cancer⁹⁻¹³.

Recent data from some of the Asian countries indicates a rapid increase in the incidence and mortality of prostate cancer¹⁴⁻¹⁶. Between 1985 and 1997, a 230% increase in prostate cancer mortality has been observed in Japanese men¹⁴. This change resembles the earlier trends of Western countries and is attributed to an aging population, environmental! dietary factors and better diagnostic methods. Since mortality from prostate cancer increases more rapidly with age than any other cancer and life expectancy in Asian men, like those in the west, is increasing, the incidence and mortality from prostate cancer is likely to increase significantly over time^{17,18}. Thus, if prostate cancer is likely to become a major health problem for Asian men it is highly desirable that appropriate measures be undertaken to diagnose and manage this disease effectively.

While the optimal treatment of prostatic cancer is debatable, radical prostatectomy has evolved as an established method to treat clinically localized prostate cancer in appropriately selected men. The major advantage of radical surgery is the high probability that the cancer can be completely removed, especially if it is confined to the prostate pathologically¹⁹.

Fifteen-year cancer specific survival rates range from 86% to 93%²⁰. With refinements in surgical technique and improved perioperative care, the morbidity of the operation has markedly decreased and the 30-day mortality in contemporary literature is less than 0.3%^{20,21}. Similarly, blood transfusion rates, mean hospital stay and cost of care has also decreased^{20,21}.

The main long-term complications relate to potency and continence. While significant urinary incontinence and anastomotic strictures are infrequent, post-operative erectile dysfunction still remains as a major morbidity of this operation.

There is limited Asian data on surgical treatment for localized prostate cancer²²⁻²⁴. We, herein, present our early results of radical retropubic prostatectomy from a single institution in men with clinical stages T1 to T2 prostate cancer.

Patients and Methods

Between December 1997 and June 2001, 23 men with clinical stage T1-2NxMo prostatic adenocarcinoma underwent PLND with or without RRP at The Aga Khan University Hospital. Clinical stages were assigned preoperatively using the TNM system. In addition to routine evaluation, all patients had digital rectal examination (DRE) and serum prostate specific antigen (PSA) estimation, (Abbott Laboratories, Chicago, IL, IMX assay) whilst

most had transrectal ultrasonography (TRUS) prior to surgery. Patients with clinical suspicion of extraprostatic extension of cancer (T3 lesions) were not considered for radical prostatectomy. The PSA levels were obtained prior to DRE or manipulation or at least 3 weeks after a prostatic biopsy or manipulation. A PSA level of 4.0 ng/ml or more was considered an abnormal result and the results obtained closest to the surgery were used as preoperative PSA values. Distant metastases were excluded by a normal radionuclide bone scan and a CT scan of the abdomen and pelvis.

Standard pelvic lymph node dissection and modified anatomical radical retropubic prostatectomy was performed²¹. We routinely perform frozen section analysis of the pelvic lymph nodes and those who had gross metastasis did not undergo radical prostatectomy, instead bilateral orchidectomy was carried out. In patients who were potent preoperatively, nerve-sparing radical prostatectomy was performed when neurovascular bundles were intraoperatively assessed to be grossly uninvolved by cancer. In patients with palpable tumor in close proximity of neurovascular bundle, the ipsilateral bundle was excised. Details of the operative findings, surgical procedure, intra and post-operative complications, blood loss and transfusions were recorded. Patients were discharged with indwelling Silicone catheter to be removed at 2 weeks in the outpatient clinic.

All prostatic biopsy specimen, whether obtained at our university or outside, were reviewed at our pathology department to confirm the presence of malignancy. The radical prostatectomy specimens were fixed en bloc in formaldehyde and painted on the outside with India ink, then sectioned. The histological grades (Gleason's primary and secondary grades) were recorded and the presence of seminal vesicle invasion, lymph nodes metastasis and tumor extension outside the surgical specimen was noted. All lymph nodes were examined for metastasis. Based on these findings, the pathologic stage was assigned according to the TNM system.

Following initial postoperative visits, the patients were followed with DRE and serum PSA levels, more or less, every 3 months for 1 year and subsequently every 6 months. Progression of the disease was defined as either clinical evidence of disease recurrence or biochemical recurrence with progressively rising PSA, with levels >0.4 ng/ml. At each visit, urinary continence, potency, development of any complication and additional treatments undertaken were noted.

Results

The mean age was 63 ± 6.2 years (median 64 years, range 51 - 76). ASA classification showed that 4% of the patients belonged to class I, 65% to class II and 31% to class III. Most patients were clinically symptomatic with 10 (44%) presenting with lower urinary tract obstructive symptoms (Table 1).

Table 1. Clinical presentation of patients with T1-2 prostate cancer.

Clinical Presentation	No.	%
Lower urinary tract obstructive symptoms	10	44
Incidentally discovered at TURP	5	22
Gross hematuria	2	09
Hemospermia	1	04
Backache	1	04
Elevated PSA only	4	17

Only 40 (17%) of the patients were asymptomatic and were diagnosed with prostate cancer following routine PSA testing.

On DRE, 3 patients (13%) had normal prostate while 20 (87%) had abnormal findings (Table 2).

Table 2. Clinical stage and pre-operative serum prostate specific antigen (PSA) levels in patients undergoing surgery with intent to treat with radical prostatectomy.

Stage	Clinical Stage		Serum PSA ng/ml	Serum PSA	
	No.	%		No.	%
T1 b NXM0	1	4	≤4	1	04
T1 c NXM0	2	9	4.1 - 10	7	31
T2 a NXM0	4	17	10.1 - 20	8	35
T2 b NXM0	5	22	20.1 - 50	3	13
T2 c NXM0	11	48	50.1 - 100	4	17

This included 4 with a unilateral nodule involving less than half of the lobe (T2a lesion), 5 with a unilateral nodule involving more than half of the lobe (T2b lesion), and 11 with bilaterally palpable nodules (T2c lesion). Patients with clinical T3 lesions were not considered for radical surgery.

Serum PSA levels were found to be elevated above normal in all cases except in one patient who was on hormonal therapy for 2 months following transurethral resection of prostate (TURP) done outside. He was taken off the hormonal therapy prior to radical prostatectomy. The mean PSA was 25 ± 29 , (median PSA = 13.7, range 1.1 -99). PSA ranges are given in

Table 2.

All patients had a negative bone scan and CT scan of the abdomen and pelvis for metastatic disease. In one case with serum PSA of 84 ng/ml, MRI bone survey and trephine bone marrow biopsy was done and was also negative for metastasis.

Five patients had evidence of nodal metastasis at frozen section. In 3 with gross metastasis RRP was abandoned and bilateral orchidectomy was carried out. While in 2 who had micro metastasis, standard RRP and bilateral orchidectomy was performed. The remaining 18 patients with no nodal metastasis underwent standard RRP (Table 3).

Table 3. Summary of operative details and length of stay in patients undergoing Surgery.

	Mean±SD	Median	Range
Operative Time (minutes)	270±65	250	170 - 360
Estimated blood loss (mls)	1097±654	1000	50 - 2200
Transfusion (Packed cell units)	2.2±1.5	2	0 - 5
Duration of hospitalization (days)	10.2±1.0	7	5 - 14

The decision to perform nerve-sparing RRP was based on pre-operative potency status and intra-operative assessment of proximity of the cancer to the neuro-vascular bundles (NVB). Of 20 cases, who had RRP 5 patients (25%) had complete bilateral NVB preservation and 7 (35%) had partial NVB preservation. In 8 patients (40%) bilateral NVB resection had to be performed in order to achieve a wide clearance margin.

Table 3 shows the operative time, estimated blood loss, transfusions, and patient's length of stay. Overall, 74% of all cases (17 of 23) and 85% of RRP cases (17 of 20) received perioperative blood transfusion. The mean transfusion requirement was 2.2 ±, 1.5 packed red cell units per patient. In RRP cases, 15% had no transfusions while 50% received 1 - 2 units, 30% had 3 - 4 units and 5% had 5 units of packed cell transfusions.

There was no mortality. Perioperative complications were observed in 3 patients (13%) including 1 case (4%) of myocardial ischaemia with no infarction and 2 cases (9%) who developed epididymo-orchitis.

Overall, 87% patients (20 of 23) are fully continent while 13% have mild to moderate stress urinary incontinence. Amongst 20 patients who underwent RRP, 85% (17 of 20) are fully continent and 15% (3 of 20) have mild to moderate stress urinary incontinence at > 6 months after surgery requiring 1 to 2 pads per day (Table 4).

Table 4. Urinary continence status and recovery of continence in patients undergoing Surgery.

	No.	%	(Cumulative %)
Total patients			
· Continent	20 of 23	87	87
· Stress Urinary Incontinence (Mild to Moderate)	3 of 23	13	100
· Severe / Total Incontinence	Nil	00	--
RRP Cases			
· Continent	17 of 20	85	85
· Stress Urinary Incontinence (Mild to Moderate)	3 of 20	15	100
· Severe / Total Incontinence	Nil	00	--
Duration to fully continent status in RRP cases			
· < 6 weeks	8 of 17	47	47
· 7 - 12 weeks	6 of 17	35	82
· 13-24 weeks	2 of 17	12	94
· > 24 weeks	1 of 17	6	100

The overall pathological staging (TNM) and grading (Gleason grading system) is shown in Table 5.

Table 5. The histopathologic grade of cancer using Gleason grading system and pathologic stage of prostate cancer based on final surgical specimen.

Gleason score			Pathologic stage		
Score	No.	%	TNM stage	No.	%
2 - 4	6	26	pT2 NoMo	12	52
5 - 7	15	65	pT2 N1Mo	1	4
8 - 10	02	09	pT3c NoMo	5	22
			pT3 N1Mo	2	9
			pTx N1Mo	3	13

At a mean follow up of 19.4 ± 13 months (median 15, range 3 - 45), 20 of 23 total patients (87%) and 17 of 20 patients who had RRP (85%) remain free of cancer sections revealed micrometastasis in pelvic lymph nodes.

In patients who underwent RRP and are continent, the mean time to return to fully continent status was 11.5 ± 11.6 weeks (median 8; range 2 - 40 weeks). The return of continence in

patients with previous TURP was 10 ± 2 weeks compared with 12 ± 13 weeks in those with no previous prostatic surgery. Three patients (15%) developed anastomotic strictures; 2 underwent optical urethrotomy and one had urethral dilation. The follow up information about potency status is available in 3 of 5 cases who had bilateral NVB preservations. Two of these 3 patients (66%) are potent.

recurrence with PSA levels 0.4 ng/ml. This is with no further cancer-related treatment except for adjuvant external beam radiation therapy in 2 cases administered on the basis of adverse histopathology. All 3 patients who failed surgical treatment (PSA >0.4ng/ml) had high-grade cancer with seminal vesicle invasion.

Discussion

Prostate cancer remains an important cause of morbidity and mortality in middle aged and elderly males. While the disease burden is far more pronounced in the western world⁴, recent data indicates a significant increase in the age-adjusted incidence and mortality rates in many Asian countries¹⁴⁻¹⁶. Unfortunately a substantial percentage of Asian men still present with regionally advanced and metastatic cancer, which remains incurable²⁵. This can be compared to the earlier pattern of disease in the western world. In the pre-PSA era of the 1970s, only 50% of the cancers detected were clinically organ-confined (clinical stage A and B, Whitmore and Jewett Classification), and 25-30% had metastases at diagnosis^{26,27}. The last 3 decades, however, witnessed major refinements in the diagnosis and treatment of prostate cancer. By utilizing the improved diagnostic techniques of regular DRE, serum PSA, transrectal ultrasound and systematic biopsies in select cases, over 90% of cancers currently diagnosed in screening studies are clinically organ-confined and 70% of those are pathologically organ confined^{6,28}. Similarly, in non screened populations, 70% of cancers detected by DRE or PSA are clinically organ-confined (T1-2,NxMo) and about half of those treated surgically are pathologically confined to the prostate (pT1-2,NoMo)²⁹. The incidence of pelvic lymph node metastasis has decreased to 5-7% in recent series of radical prostatectomy^{30,31}. This demonstrates a remarkable stage migration with an increasing percentage of localized cancers being diagnosed in younger men, amenable to potentially curative treatment.

Similarly, marked advancements have taken place in improving the techniques of potentially curative treatment options of radical prostatectomy and radiation therapy. Reiner and Walsh³² described the anatomical RRP with delineation and control of dorsal venous complex. This led to marked reduction in intraoperative blood loss, which used to be a major morbidity of this operation. Subsequently, Walsh and Donker³³ defined the anatomy of the cavernosal nerves and pelvic plexus. With nerve-sparing operation³⁴, it has become possible to preserve sexual function in a substantial percentage of appropriately selected patients without compromising cancer control. A much improved understanding of the anatomy of striated urethral sphincter has also led to modifications in surgical technique with subsequent reduction in the frequency of postoperative urinary incontinence.³⁵

The major advantage of surgery in the treatment of clinically localized prostate cancer is the high probability that the cancer would be completely removed, especially if it is confined within the prostate pathologically^{19,36}. In modern series, 80% of patients with clinical stage T1-2, NxMo prostate cancer treated with radical prostatectomy have no evidence of progression at 5 years as assessed by PSA estimation and 70% are free of progression at 10

years²¹. Radical surgery, however, has its associated morbidity and mortality though markedly decreased than before. Postoperative mortality is rare, accounting for 0.2% to 0.7% in large contemporary series. Serious morbidity (myocardial infarction, pulmonary embolism, pneumonia) occurs in 2 to 3% and the need for a blood transfusion is in about 10% cases³⁷. Therefore, the risk-benefit analysis is crucial while formulating treatment plan for an individual patient with prostate cancer.

Radical prostatectomy should be considered for men with clinically localized prostate cancer if they are in good general health and have a life expectancy of 10 years or longer. The risk of spread of cancer with conservative treatment needs to be assessed against the potential side effects of radical surgery. Thus, the most important factors that influence the risk-benefit analysis include the age and general health of the patient, the extent of cancer involvement (PSA, grade, stage) and the potential of cure and complications with surgical treatment²⁰.

Our small series confirms the excellent cancer control potential of this operation, although the patients need a longer follow-up. The effective management of prostate cancer in a developing country, however, remains far from acceptable. For a variety of reasons, there are no concerted efforts to diagnose this cancer at an earlier stage. Thus, most patients in Pakistan still present with locally advanced or metastatic cancer and cannot be considered for curative treatment. Even, in our select group of T₁-2 cancer cases, most patients had a significant disease burden with bilateral prostatic nodularity (cT₂c stage) present in 48% of cases. Only 9% of the cases in our series were T₁c cancers, (elevated PSA and normal DRE). This contrasts remarkably with the western series where T₁c cancers account for upto half of all treated cases.^{19,34,36} In our early experience, the blood transfusion rate and the length of stay is higher than the contemporary series,^{19,34,36} which hopefully would improve with increasing experience. Our cancer control rate, return of urinary continence and potency data compares favorable with the contemporary data.^{19,34,36,37} A higher than expected percentage of our patients developed anastomotic strictures, which could be related to previous TURP in one of three such cases. Despite most cases having an ASA II and III status, we fortunately did not encounter any serious complications or perioperative mortality.

In conclusion, radical prostatectomy appears to be generally safe and can effectively eradicate cancer in a large proportion of patients. With refinements in surgical technique and improved anesthesia facilities, the surgery related morbidity and mortality has markedly decreased. We recommend radical prostatectomy as a potentially curative option in select men with localized prostate cancer.

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