

Surgical and Oncological Outcomes in Patients with Preoperative PSA >20 ng/ml Undergoing Robot-assisted Radical Prostatectomy

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Abstract. *Background:* The objective of this study was to assess the surgical and the oncological outcomes in patients with a preoperative prostate specific antigen (PSA) value >20 ng/ml, undergoing robot-assisted radical prostatectomy (RARP) for prostate cancer. *Patients and Methods:* The records of 2000 men who underwent RARP from February 2006 to April 2010 were retrospectively reviewed. A total of 147 (7.3%) patients with a preoperative PSA value >20 ng/ml were identified. A comparison was performed between the overall patient cohort and the patients with PSA >20 ng/ml. The analyzed parameters included: minor and major postoperative complications, postoperative Gleason score, pathological stage, positive margins and lymph node status, as well as biochemical progression and disease-specific mortality during the follow-up period. *Results:* The following results reflect the comparison of the overall cohort of patients vs. the cohort of patients who had a preoperative PSA >20ng/ml. A statistical difference of the analyzed parameters was observed for median PSA value 10.3 ng/ml vs. 34.8 ng/ml ($p<0.05$), for bilateral neurovascular bundle preservation 65.7% vs. 19.7% ($p<0.001$), for a Gleason score <7, 42.8% vs. 12.9% ($p<0.05$) and for a Gleason score >7 in 9.5% vs. 19.7% ($p<0.05$). Organ-confined disease was noted in 73.5% vs. 31.9% ($p<0.05$) and extraprostatic extension in 25.2% vs. 86.1% ($p<0.05$). The percentage of

cancer found in the prostate specimen was 16.1% vs. 38.1% ($p<0.05$) and a positive surgical margin (PSM) status was encountered in 8.9% vs. 33.3% ($p<0.05$) of patients. Positive lymph nodes were encountered in 3.2% vs. 17.1% of patients ($p<0.05$). After a median follow-up of 19.6 months (range 3-56 months), 118 patients (80.2%) were free of biochemical progression and no disease-specific mortality was evident. *Conclusion:* Although RARP in patients with preoperative PSA >20 ng/ml is a safe surgical procedure with limited complications, the risk of positive lymph nodes, as well as the PSM status are found to be significantly higher. Patients should be informed of these probable outcomes, as well as for a possible need for adjuvant treatment before undergoing the procedure.

Prostate specific antigen (PSA) is the central component in virtually all models predicting pathological stage and grade in regard to radical prostatectomy (1). After the introduction of PSA into clinical practice, the urological community experienced a dramatic shift towards more localized and therefore, curable prostate cancer (PCa). Nevertheless, up to 10% of patients are still considered as high-risk patients. Given the fact that PSA screening detects patients with PCa earlier in their disease course, there has been a steady decline in the numbers of patients presented with PSA levels >20 ng/ml. Hugosson *et al.* (2) demonstrated that PSA levels of 20 to 99.9 ng/ml and >100 ng/ml occurred only in 0.5% and 0.04% of screened men, respectively. Despite these trends towards lower-risk PCa, as many as 20% to 35% of patients with newly diagnosed PCa are still classified as being at high risk, based on either a Gleason score of 8 to 10, a PSA >20 ng/ml, or an advanced clinical stage (3). This is of particular concern for patients without evidence of distant metastases presented with initial PSA >20 ng/ml. Since these patients are estimated to have a poorer prognosis compared with those with lower PSA levels, it is difficult to select the optimal

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treatment modality (4). Although there is no consensus regarding the optimal treatment of men with high-risk PCa, external beam radiotherapy and radical prostatectomy are the options most physicians, who commonly treat high-risk PCa, would recommend (5). Recent surgical series have demonstrated 10-year cancer-specific survival rates between 72% and 92% for men with high-risk disease. This indicates that the majority of men with high-risk PCa, including those with very high PSA levels, stand to benefit from radical prostatectomy (6-8). During recent years, robot-assisted laparoscopic radical prostatectomy (RARP) has become profoundly popular among urologists for the treatment of localized PCa. Although there might be a lack of randomised trials, there is reasonable evidence to suggest that RARP is a well-tolerated, safe, and efficacious intervention for the management of localised PCa (9, 10). Furthermore, RARP is an appealing treatment option for clinically localized PCa due to fast recovery, less blood loss, improved cosmesis and surgical outcomes comparable to those of open radical prostatectomy. The objective of this study was to evaluate the surgical and oncological outcomes in men with PSA values >20 ng/ml undergoing RARP.

Patients and Methods

The records of 2000 men who underwent RARP from February 2006 to April 2010 were retrospectively reviewed. All perioperative and postoperative data prospectively recorded in our database. A total of 147 (7.3%) patients with a preoperative PSA value >20 ng/ml were identified. A comparison was performed between the overall patient cohort and the aforementioned patients. RARP was performed using the Da Vinci Robotic 4-Arm System (Intuitive Surgical, Sunnyvale, California) *via* a transperitoneal approach. Pelvic lymph node dissection was performed in all patients. Bilateral neurovascular bundle (NVB) preservation was attempted in patients with a Gleason score ≤ 7 . Men with preoperative impotence did not undergo NVB preservation. The procedures in both patient cohorts were performed by five experienced RARP surgeons by a standard transperitoneal approach as reported previously by our group (11).

The compared parameters between the two groups included patients' preoperative clinicopathological characteristics [age, body mass index (BMI), prostate size and PSA values], intraoperative characteristics [NVB preservation, estimated blood loss, and skin-to-skin operative time], postoperative oncological characteristics [tumor volume, Gleason score, pathological stage, positive surgical margins (PSM) and lymph node status], minor complications [retention, urinary leakage, urinary tract infection, lymphocele, superficial abscess and subcutaneous emphysema], major complications [infected lymphocele, bowel injury, acute renal failure and re-operation], duration of catheterization, biochemical progression and disease-specific mortality during the follow-up period. Postoperative complications and re-interventions encountered up to 30 days postoperatively, were stratified by the Clavien classification (12) and were characterized as minor (Clavien's grade I-IIIa) and major (Clavien's grade IIIb-IVa) postoperative complications. Hemorrhage was defined as greater than 500 ml blood loss during the operation. PSM was defined as

tumor at the inked surface of the specimen. The site (apex or basis) and the amount (single or multiple) of PSM encountered was not reviewed. The biochemical progression was defined as PSA ≥ 0.2 ng/ml after nadir or never reaching nadir. In all patients, after surgery was performed, only PSA surveillance was performed with deferred external radiation therapy and/or hormonal therapy at the onset of a rise in PSA. In these cases, adjuvant therapy was initiated, and patients were further excluded from the follow-up biochemical progression but not from that for disease-specific mortality.

All patients underwent cystography at postoperative day four. The catheter was then removed if no extravasation was recorded. If extravasation was present, the catheter was left in place for seven additional days. The median postoperative follow-up for the patients was 19.6 months (range 3-56 months). For comparison between two groups of continuous values the Student *t*-test was used. For comparison between three or more groups one-way ANOVA, with the Tukey correction for multiple comparisons, was used. For comparison of binomial values, the Chi-Square test was used. Simple linear regression was used to test the effect of one continuous parameter against another. A *p*-value of <0.05 was considered significant.

Results

The preoperative, intraoperative and postoperative clinicopathological characteristics of the two groups are listed in Table I. The following results reflect the comparison of the overall cohort of patients *vs.* the cohort of patients who had a preoperative PSA >20 ng/ml. A statistical difference of the analyzed parameters was observed in the median PSA value, 10.3 ng/ml *vs.* 34.8 ng/ml ($p < 0.05$), in the bilateral NVB preservation 65.7% *vs.* 19.7% ($p < 0.001$), in Gleason score <7, 42.8% *vs.* 12.9% ($p < 0.05$) and in Gleason score >7 in 9.5% *vs.* 19.7% ($p < 0.05$). Organ-confined disease was noted in 73.5% *vs.* 31.9% ($p < 0.05$), extraprostatic extension in 25.2% *vs.* 86.1% ($p < 0.05$). The PSM status was encountered in 8.9% *vs.* 33.3% ($p < 0.05$) of patients. Pelvic lymph node dissection was performed in 1623 patients (81.2%) of the overall cohort, out of whom 64 cases (3.2%) were positive for metastasis. In the patient cohort with PSA >20 ng/ml, pelvic lymph node dissection was performed in all 147 patients (100%), out of whom in 25 cases (17.1%) it was positive for metastasis ($p < 0.05$).

Major complications were noted in 1.3% *vs.* 0.6% of cases. One patient (0.6%) from the patient cohort with PSA >20 ng/ml exhibited a major complication, which was an infected lymphocele that was identified and treated conservatively. Minor complications were encountered in 11.4% *vs.* 13.6% of the patients. Twenty patients (13.6%) from the patient cohort with PSA >20 ng/ml, exhibited minor complications, which were urinary leakage (seven patients 4.7%) which was treated with leaving the catheter in place for an additional seven days; urinary retention (seven cases, 4.7%), which was treated by inserting a new catheter and removing it two days later; asymptomatic lymphocele in five patients (3.4%), which was treated conservatively, and one

Table I. Preoperative, intraoperative and postoperative clinicopathological characteristics of the two groups analysed in the study.

Parameters	Overall patient cohort	PSA value >20 ng/ml	p-Values
Patients	2000	147	
Age in years	63 (38-79)	63.1 (47-79)	
Body Mass Index	26.7 kg/m ² (19-51 kg/m ²)	27.2 kg/m ² (29-37 kg/m ²)	
Prostate size	56.1 g (10-170 g)	62.8 g (28-116 g)	
Prostate specific antigen (PSA)	10.3 ng/ml (0.3-220 ng/ml)	34.8 ng/ml (20.1-220 ng/ml)	<0.05
Neurovascular bundle preservation	65.7%	19.7%	<0.001
Blood loss	160 ml (60-1500 ml)	183 ml (50-1500 ml)	
Minor complications	11.4%	13.6%	
Major complications	1.3%	0.6%	
Operative time	156 min (80-465 min)	164 min (100-360 min)	
Length of catheterisation	5.5 days (5-31 days)	5.7 days (5-26 days)	
Gleason score			
<7	2.8%	12.9%	<0.05
=7	47.7%	60.5%	
>7	9.5%	19.7%	<0.05
Stage			
Confined disease	73.5%	31.9%	<0.05
Extraprostatic extension	25.5%	86.1%	<0.05
Positive margins	8.9%	33.3%	<0.05
Tumor in specimen %	16.1% (1-99%)	38.1% (1-96%)	<0.05
Positive lymph nodes	3.2%	17.1%	<0.05

patient (0.6%) with a symptomatic urinary infection which was treated conservatively. After a median follow-up of 19.6 months (range 3–56 months), for which 103 patients (70.3%) had a follow-up of more than 12 months (median 24.6 months), 118 patients (80.2%) of the patient cohort who had a preoperative PSA >20 ng/ml, were free of biochemical progression and no disease-specific mortality was evident.

Discussion

Although there is no consensus regarding the optimal treatment of men with high-risk PCa, external beam radiotherapy and radical prostatectomy are the options most physicians, who commonly treat high-risk PCa, would recommend (5). Recent studies have indicated that the majority of men with high-risk PCa, including those with very high PSA levels, stand to benefit from radical prostatectomy (6-8). Zwergel *et al.* (13) retrospectively assessed the outcome of 275 patients with an initial PSA of 20 ng/ml, or higher, who underwent radical prostatectomy for PCa. Biochemical progression occurred in 92 patients (33.5%). Overall (and disease-specific) survivals at 5, 10, and 15 years were 87% (93%), 70% (83%), and 58% (71%), respectively. They concluded that according to long-term follow-up results in this high-risk cohort of patients, with preoperative PSA 20 ng/ml or higher, radical prostatectomy can be considered a viable therapeutic option. Likewise, Inman *et al.* (14) evaluated the long-term outcomes of 236

men with PCa and very high (≥ 50 ng/ml) PSA values that were treated with radical prostatectomy. Biochemical recurrence-free survival rates in the groups of patients with a PSA levels of 50 to 99 ng/ml and ≥ 100 ng/ml were 43% and 36% at 10 years, respectively. Systemic progression-free survival rates in the PSA 50 to 99 ng/ml and PSA ≥ 100 ng/ml groups were 83% and 74% at 10 years, respectively. The estimated overall cancer-specific survival was 87% at 10 years. They concluded that patients with PCa and serum PSA levels ≥ 50 ng/ml have very high-risk PCa that carries a high likelihood of being pathologically advanced. Although the probability of realizing long-term survival in these high-risk patients is less than in patients with more favourable disease, 10-year survival outcomes remain excellent and argue for aggressive management of these cases.

Furthermore, Nguyen *et al.* (15) assessed the cancer control afforded by radical prostatectomy in 41 patients with PSA values >20 ng/ml. The mean PSA was 27.39 ± 13.57 ng/ml (range 20.3-80 ng/ml). After pathological analysis, PCa was found to be organ confined in 51.2% of cases and locally advanced in 20 cases 48.8% of cases. Positive surgical margins were detected in 36.5% of cases. Lymph node involvement was evident in 12% of cases. Similar results were also evident in our patient cohort. The median time to biochemical recurrence was 44.6 ± 22 months. The 5-year PSA-free survival rate was 53%. They concluded that radical prostatectomy can be recommended as a viable primary treatment option in selected cases of high-risk patients with preoperative PSA values >20 ng/ml. Other

authors have also reported similar results. D'Amico *et al.* (16) found that men with PSA levels >20 ng/ml had a >50% risk of PSA failure at 5 years. In the study of Han *et al.* (17), 120 men with palpable disease (cT2a to cT3a) and preoperative PSA values >15 ng/ml demonstrated overall PSA-free survival rates at 5 years and 10 years of 56% and 40%, respectively. Finally, May *et al.* (18) found a higher PSA failure rate, with only 27% of their patients, having PSA values of 50.1 ng/ml to 100 ng/ml, remaining PSA-free at 5 years.

The fact that men with PCa and high PSA levels stand to benefit from radical prostatectomy is an established factor. The outcomes of such patients undergoing RARP remains to be shown, but would probably be similar to that of open radical prostatectomy. As seen from the results of our patient cohort, after a median follow-up of 19.6 months (range 3-56 months), 118 patients (80.2%) were free of biochemical progression and no disease-specific mortality was evident.

To our knowledge, this is the first study evaluating the surgical and oncological outcomes in men with PSA >20 ng/ml undergoing RARP. Although our study benefits from reporting on a large cohort of patients with a PSA value >20 ng/ml undergoing RARP, there are two severe limitations that should be addressed. The first is that there was an inadequate follow-up period regarding the PSA-free survival and the disease-specific survival. The second is the fact that although a PSM status was found in 33.3% of patients, its anatomical location (apex, middle, base) and its amount (millimetres of PSM encountered) was not reviewed. PSM is a known statistically significant prognostic factor, but it has not been proven to independently predict local relapse. The majority of patients with PSM (50% to 60%) will not experience clinical disease progression, even without adjuvant therapy (19). However, multiple PSM or positive margins at the prostatic base have been associated with a significantly increased risk of biochemical recurrence (20, 21).

Despite these limitations and although RARP in patients with a preoperative PSA value >20 ng/ml is a safe surgical procedure with limited complications, the risk of positive lymph nodes, as well as PSM, is significantly higher. Patients should be informed of these probable outcomes, as well as of a possible need for adjuvant treatment before undergoing the procedure.

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