

Surgical and Oncological Outcomes in Patients with a Preoperative PSA Value <4 ng/ml Undergoing Robot-assisted Radical Prostatectomy

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Abstract. *Background:* The objective of this study was to assess the surgical and oncological outcomes in patients with a preoperative prostate specific antigen (PSA) value <4 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 169 (8.4%) patients with a preoperative PSA value <4 ng/ml were identified. A comparison was performed between the overall patient cohort and the aforementioned patients. The analyzed parameters included: minor and major postoperative complications, postoperative Gleason score, pathological stage, positive margin status as well as presence of biochemical progression and of 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 value <4 ng/ml. A statistical difference of the analyzed parameters was observed in the median PSA value; 10.3 ng/ml (0.3-220 ng/ml) vs. 2.8 ng/ml (0.3-3.9 ng/ml) ($p<0.001$), in bilateral NVB; 65.7% vs. 85.2% ($p<0.001$), in Gleason score <7; 42.8% vs. 59.1% ($p<0.05$), in Gleason score 7; 47.7% vs. 36.6% ($p<0.05$) and in Gleason score >7 in 9.5% vs. 3.5% ($p<0.001$). Organ-confined disease was noted in 73.5% vs. 86.3% ($p<0.05$), extraprostatic extension in 25.2% vs. 13.7% ($p<0.05$). The percentage of cancer

*found in the prostate specimen was 16.1% (1-99%) vs. 7.3% (1-96%) ($p<0.05$) and a positive surgical margin status was encountered in 8.9% vs. 4.7% ($p<0.05$) 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 of PSA value <4 ng/ml, pelvic lymph node dissection was performed in 114 patients (67.4%), out of which one case (0.5%) was positive for metastasis ($p<0.05$). After a median follow-up of 24.2 months (range 3-56 months), 162 patients (95.8%) were free of biochemical progression and no disease-specific mortality was evident. *Conclusion:* RARP in patients with a preoperative PSA value <4 ng/ml is a safe surgical procedure with limited complications and excellent oncological outcome.*

An elevated prostate-specific antigen (PSA) level is a significant predictor of prostate cancer (PCa) (1). The advent of PSA use has changed the diagnosis of PCa and the incidence of early cancer has increased dramatically in both asymptomatic screened populations and symptomatic referral populations (1). Although PSA is recognized as a serum marker with high sensitivity and the value of 4.0 ng/ml is considered as an appropriate cut-off for biopsy, data suggest that a cut-off of PSA greater than 2.5 ng/ml has a predictive value similar to the one of PSA greater than 4.0 ng/ml, and improves treatment outcomes in screened populations (2-4). Indeed, studies have shown that the prevalence of overall and high grade PCa is 5.2% and 24.7% among men with PSA values of 2.1 to 4.0 ng/ml, respectively (5). Studies have also demonstrated that highly undifferentiated PCa produces proportionally less PSA compared with well-differentiated tumors, suggesting that low PSA levels may be associated with high-grade disease (6). Furthermore, some studies have found that men who have normal PSA levels have the same or a higher risk of PSA failure after undergoing radical prostatectomy compared with men who have higher PSA

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levels (7-9). However, most series have shown that men with normal PSA levels have improved oncological outcomes relative to the outcomes of men with slightly elevated PSA levels (9-11). Indeed, after almost two decades of PSA screening, mortality from PCa has decreased, but it is not well known if the mortality reduction is due to screening or to other factors, such as surgical treatment (10-12). Regarding the surgical treatment efficacy, various studies have reported on excellent oncological and survival outcomes in patients with PCa and low PSA levels, who underwent radical prostatectomy (4, 13-14).

In the 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 (15, 16). Furthermore, RARP is an appealing treatment option for clinically localized PCa due to fast recovery, less blood loss, improved cosmesis and surgical outcomes as comparable to those of open radical prostatectomy. The objective of this study was to evaluate the surgical and oncological outcomes in men with a PSA value <4 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 were prospectively recorded in our database. A total of 169 (8.4%) patients with a preoperative PSA value <4 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, CA, USA) *via* a transperitoneal approach. Pelvic lymph node dissection was performed in patients with a Gleason score >6 or a positive digital rectal examination. 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 previously reported by our group (17).

The parameters compared between the two groups included patient 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 and positive surgical margins (PSM)], minor complications [retention, urinary leakage, urinary tract infection, lymphocele, superficial abscess and subcutaneous emphysema] and 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 (18) and were characterized as minor (Clavien's grade I-IIIa) and as major

postoperative complications (Clavien's grade IIIb-IVa). 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. 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 cases where an adjuvant therapy was initiated, these patients were further excluded from the follow-up of biochemical progression but not from that of disease-specific mortality follow-up.

All patients underwent cystography at postoperative day 4. The catheter was then removed if no extravasation was recorded. If extravasation was present, the catheter was left in place for an additional seven days. The median postoperative follow-up of the patients was 24.2 months (range 3-56). For comparisons between the two groups of continuous values the Student *t*-test was used. For comparisons between three or more groups, one-way ANOVA with 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 value <4 ng/ml. A statistical difference of the analyzed parameters was observed in the median PSA value 10.3 ng/ml *vs.* 2.8 ng/ml (*p*<0.001), in bilateral NVB preservation 65.7% *vs.* 85.2% (*p*<0.05), in Gleason score <7, 42.8% *vs.* 59.1% (*p*<0.05), in Gleason score 7, 47.7% *vs.* 36.6% (*p*<0.05) and in Gleason score >7 in 9.5% *vs.* 3.5% (*p*<0.001). A organ-confined disease was noted in 73.5% *vs.* 86.3% (*p*<0.05), extraprostatic extension in 25.2% *vs.* 13.7% (*p*<0.05). PSM status was encountered in 8.9% *vs.* 4.7% (*p*<0.05) of patients. Pelvic lymph node dissection was performed in 1623 patients (81.2%) of the overall cohort, out of which 64 cases (3.2%) were positive for metastasis. In the patient cohort with a PSA value <4 ng/ml, pelvic lymph node dissection was performed in 114 patients (67.4%) of which, one case (0.5%) was positive for metastasis (*p*<0.05).

Major complications were noted in 1.3% *vs.* 1.7% of the cases. Three patients (1.5%) from the patient cohort with PSA <4 ng/ml, exhibited a major complication, which was an infected lymphocele in one patient (0.5%), that was identified and treated conservatively. One patient (0.5%) exhibited a secondary partial anastomosis rupture with peritonitis, which was also identified and treated conservatively and one patient (0.5%) exhibited a large perivesical hematoma, which was treated surgically. Minor complications were encountered in 11.4% *vs.* 7.1% of the patients. Twelve patients (7.1%) from the patient cohort with a PSA value <4 ng/ml, exhibited minor complications which were urinary leakage in six patients (3.5%), treated with

Table I. Preoperative, intraoperative and postoperative clinicopathologic characteristics of the two groups

Parameters	Overall patient cohort	PSA value < 4 ng/ml	p-values
Patients	2000	169	
Age in years	63	62	
Body Mass Index	26.7 kg/m ²	26.8 kg/m ²	
Prostate size	56.1 gr.	48.7 gr.	
Prostate specific antigen	10.3 ng/ml (0.3-220 ng/ml)	2.8 ng/ml (0.3-3.9 ng/ml)	<0.001
Neurovascular bundle preservation	65.7%	85.2%	<0.05
Blood loss	160 ml	172 ml	
Minor complications	11.4%	7.1%	
Major complications	1.3%	1.7%	
Operative time	156 min	158 min	
Length of catheterisation	5.5 days	5.6 days	
Gleason score			
<7	42.8%	59.1%	<0.05
=7	47.7%	36.5%	<0.05
>7	9.5%	3.5%	<0.05
Stage			
Confined disease	73.5%	86.3%	<0.05
Extraprostatic extension	25.5%	13.7%	
<0.05			
Positive margins	8.9%	4.7%	<0.05
Tumor in specimen %	16.1% (1-99%)	7.3% (1-96%)	
Positive lymph nodes	3.2%	0.5%	<0.05

leaving the catheter in place for an additional seven days, urinary retention in four cases (1.1%), which was treated by inserting a new catheter and removing it two days after and a symptomatic urinary infection in one patient (0.5%), which was treated conservatively. After a median follow-up of 24.2 months (range 3-56 months) for which 135 patients (79.8%) had a follow-up of more than 12 months (median \pm 28.4 months), 162 patients (95.8%) of the patients cohort who had a preoperative PSA <4 ng/ml were free of biochemical progression, while no disease-specific mortality was evident.

Discussion

The PSA level is the most commonly used tumor marker for PCa. Historically, a PSA level >4.0 ng/ml has been considered abnormal. During the past decade though, a high frequency of PCa in men with PSA levels less than 4.0 ng/ml has been evident. A study from the Prostate Cancer Prevention Trial confirmed that PCa with low PSA is common, and demonstrated that tumors in men with low PSA levels appeared more often to be low grade, disease of low clinical stage than in men screened with higher PSA (5). This phenomenon was also observed in our cohort of patients.

Although most studies have found that men with normal PSA levels have better outcomes after radical prostatectomy relative to men with slightly elevated PSA levels (19, 20), others have found that men with normal PSA levels had poorer outcomes. Stamey *et al.* found that among men with

PSA levels <4 ng/ml, approximately 30% had no evidence of Gleason pattern 4 or 5 tumors in RP specimens, compared with 20% of men with PSA levels of 4 to 9 ng/ml and 8% of men with PSA levels of 9 to 22 ng/ml (9). Similarly, D'Amico *et al.* found that 25% of men with PSA levels of 4 to 10 ng/ml had biopsy Gleason scores \geq 7 compared with only 20% of men with PSA levels <4 ng/ml (7). Kobayashi *et al.* reported that the detection rate of PCa was 23.6% both in the group with PSA of 2.0 to 4.0 ng/ml and in the group with PSA of 4.1 to 10.0 ng/ml, while no difference in pathological features was found (21). Park *et al.* also reported that there was no difference in the detection rate of PCa and its pathological features between the group with PSA of 3.0 to 4.0 ng/ml and the group with PSA of 4.1 to 10.0 ng/ml (22).

The Prostate Cancer Prevention Trial (5), study corroborates the observation that PCa with low PSA is, on average, smaller and of lower Gleason score than tumors occurring in men with increased PSA (greater than 4.0 ng/ml) at diagnosis. This observation is consistent with the notion that the amount of PSA found in the serum is proportional to the mass of the prostatic cells that produce PSA and that small tumors are less likely to produce higher levels of PSA than larger tumors. Furthermore, they observed that patients with low screening serum PSA tended to be younger (younger than 62 years at diagnosis), and to have smaller, lower grade and lower stage tumors that are amenable to surgical excision. These patients did extremely well, with low

rates of PSA recurrence or clinical evidence of recurrent disease. Similar results were also found in this study. The median age of the patients was 62 years, the patients exhibited lower grade and lower stage tumors and PSM status was encountered in 4.7% vs. 8.9 % of patients. After a median follow-up of 24.2 months, 162 patients (95.8%) of the cohort with PSA <4 ng/ml, were free of biochemical progression.

Zhu *et al.* compared the pathological outcomes and the PSA progression rates of patients who underwent radical prostatectomy because of PCa, whose cancer was detected at a PSA level of 2.6 to 4.0 ng/ml *versus* those with cancer detected after the PSA level rose to greater than 4.0 ng/ml (23). They evaluated 223 patients who underwent radical prostatectomy and had a preoperative PSA level of 2.6 to 4.0 ng/ml and 74 who had a preoperative PSA level greater than 4.0 ng/ml. The median follow-up was four years. The patients with a preoperative PSA level between 2.6 and 4.0 ng/ml had more favorable pathological outcomes in terms of cancer volume, pathological stage, and of possibly rapidly progressive cancer rate. The possibly insignificant cancer rates were not different between the groups. A trend was noted for patients with a preoperative PSA level between 2.6 and 4.0 ng/ml, to have a lower PSA progression rate.

Treatment decision-making in patients with localized PCa with a low PSA value is complex. Shao *et al.* (24) reported on treatment patterns among men diagnosed as having PCa and a PSA level <4.0 ng/ml. They revealed that men with a PSA level of 4.0 ng/ml or lower represent 14% of the incident PCa cases; 54% of men diagnosed as having PCa and PSA levels lower than 4.0 ng/ml harbor low-risk disease (stage \leq T2a, PSA level, \leq 10 ng/ml, and Gleason score \leq 6), but over 75% of them underwent radical prostatectomy or radiotherapy. Regarding surgical treatment efficacy, various studies have reported on excellent oncological and survival outcomes of patients with PCa with low PSA levels who underwent radical prostatectomy (4, 13, 14).

During recent years 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 (15, 16). 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.

To our knowledge, this is the first study ever to evaluate the surgical and oncological outcomes in men with PSA values <4 ng/ml undergoing RARP. Although our study benefits from reporting on a large cohort of patients with a PSA value <4 ng/ml, there is one severe limitation that should be addressed. There was an inadequate follow-up period regarding PSA-free survival and disease-specific

survival. Despite this limitation, our findings suggest that RARP in patients with a preoperative PSA value <4 ng/ml is a safe surgical procedure with limited complications and excellent oncological outcomes.

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