

## Robotic-assisted Radical Prostatectomy in Men $\leq 50$ Years of Age. Surgical, Oncological and Functional Outcomes

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**Abstract.** *Background:* The aim of this study was to evaluate the surgical, oncological and functional outcomes in men  $\leq 50$  years of age treated with robot-assisted laparoscopic radical prostatectomy (RARP). *Patients and Methods:* The records of 2000 men who underwent RARP from February 2006 to April 2010 were retrospectively reviewed. A total of 68 patients who were  $\leq 50$  years of age were indentified. 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, continence and potency 12 months after treatment and presence of 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 were  $\leq 50$  years of age. A statistical difference of the analyzed parameters was observed in prostate weight 56.1 g vs. 31.4 g ( $p < 0.05$ ), in bilateral neurovascular bundle (NVB) preservation 65.7% vs. 92.6% ( $p < 0.05$ ), and in oncological and functional outcomes. Organ-confined disease was noted in 73.5% vs. 78.5% ( $p < 0.05$ ), extraprostatic extension in 25.2% vs. 21.5% ( $p < 0.05$ ) and positive surgical margins were encountered in 8.9% vs. 5.8% ( $p < 0.05$ ). A Gleason score  $< 7$  was noted in 42.8% vs. 54.4% ( $p < 0.05$ ), a Gleason score 7 in 47.7% vs. 41.2% ( $p < 0.05$ ) and a Gleason score  $> 7$  in 9.5% vs. 4.4% ( $p < 0.05$ ). At 12 months, 92.8% vs. 95.5% were continent and 66.2% vs. 93.7% ( $p < 0.001$ ) were potent. After a median follow-up of 17.8 months, 97.1% patients of the  $\leq 50$  years

patient cohort were free of biochemical progression and no disease-specific mortality was evident. *Conclusion:* Our findings suggest that RARP in patients  $\leq 50$  years of age is a safe surgical procedure with limited complications and excellent oncological and functional outcomes. Although the preservation of the NVB in such patients is preferable, this can be performed without compromising the radical nature of cancer surgery.

Although prostate cancer (PCa) has traditionally been regarded as a disease of older men, according to data from the Surveillance, Epidemiology, and End Results (SEER) database, the earliest cancer-related deaths are in men aged 35 to 44 years (1). Guidelines from the American National Comprehensive Cancer Network recommend screening for prostate-specific antigen (PSA) in men starting from the age of 40, with retesting either annually or at the age of 45 depending on the initial test value, on the basis of findings in two retrospective cohorts that an increased PSA in the fourth decade increased the risk of PCa (2, 3). Following the large-scale use of PSA and the development of screening methods, more and more patients are diagnosed with PCa at earlier ages. Once more, data from the SEER show that during the 1970s, patients of less than 50 years of age, represented only 1% of the diagnosed cases and in 2005, this number had reached 4% (4). It is controversial whether PCa in younger men has less favourable outcome than in older men. While previous studies point to a relationship between younger men and more advanced tumors, which suggests that those would not be ideal candidates for radical prostatectomy (6-8), more recent studies, show that younger individuals present a greater probability of organ-confined tumors and higher disease-control rates when submitted to radical prostatectomy (4, 9-10). Literature lacks knowledge on treatment preferences and decision-making in young PCa patients. Sidana *et al.* (11) evaluated 986 men under 50 years of age, diagnosed with PCa between 2001 and 2005. They discovered that the most common primary therapy was surgery in 81.4%.

During recent years, robot-assisted laparoscopic radical prostatectomy (RARP) has become profoundly popular

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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 (12, 13). 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, oncological and functional outcomes in men  $\leq 50$  years of age 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 recorded prospectively in our database. A total of 68 (3.4%) patients who were  $\leq 50$  years of age 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 prostate specific antigen (PSA) level  $>10$  ng/ml and/or Gleason score  $>6$ . Bilateral neurovascular bundle (NVB) preservation was attempted in patients with a PSA level  $<10$  ng/ml and/or Gleason score  $\leq 7$ . Men with preoperative impotence did not undergo NVB preservation. Patients who underwent a unilateral or a non nerve-sparing surgery were excluded from the sexual function analysis. The procedures in both patient cohorts were performed by five experienced RARP surgeons by a standard transperitoneal approach as reported previously by our group (14).

The compared parameters between the two groups included patient preoperative clinicopathologic 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, continence, potency, 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 (15) and were characterized as minor (Clavien's grade I-IIIa) or 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 oncological results were evaluated by staging the operative specimens according to the TNM 2002 classification. Biochemical progression was defined as PSA  $\geq 0.2$   $\mu\text{g/l}$  after nadir or never reaching nadir. In all patients, after surgery, 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, an adjuvant therapy was initiated, and those patients were further excluded from the follow-up biochemical progression but not from that for the 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. Functional results regarding urinary continence were evaluated prospectively only 12 months after surgery. Urinary continence was defined as no pad use and/or no urinary leakage. Functional results regarding potency were evaluated prospectively only 12 months after surgery. Potency was defined as erections sufficient for penetration, with or without phosphodiesterase inhibitors. The analysis of potency was limited to patients who were potent before RARP, had bilateral nerve-sparing surgery, and had a follow-up of  $\geq 12$  months with no adjuvant therapy. Once a patient was potent or continent, he was considered potent or continent on further analysis. The median postoperative follow-up of the patients was 17.8 months (range 3-49 months). For the 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 the 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 were  $\leq 50$  years of age. A statistical difference of the parameters analyzed was observed in the age of the patients 63 *vs.* 48 years old ( $p < 0.05$ ), in prostate weight 56.1 g *vs.* 31.4 g ( $p < 0.05$ ), in bilateral NVB preservation 65.7% *vs.* 92.6% ( $p < 0.05$ ), in organ-confined disease 73.5% *vs.* 78.5% ( $p < 0.05$ ), in extraprostatic extension 25.2% *vs.* 21.5% ( $p < 0.05$ ), positive surgical margins were encountered in 8.9% *vs.* 5.8% ( $p < 0.05$ ), a Gleason score  $< 7$  was noted in 42.8% *vs.* 54.4% ( $p < 0.05$ ), a Gleason score 7 in 47.7% *vs.* 41.2% ( $p < 0.05$ ), a Gleason score  $> 7$  in 9.5% *vs.* 4.4% ( $p < 0.05$ ) and the potency at 12 months was 66.2% *vs.* 97.3% ( $p < 0.001$ ).

The median PSA value was 10.3 ng/ml *vs.* 8.3 ng/ml. Major complications were noted in 1.3% *vs.* 1.4% of cases. One patient (1.4%) from the younger patient cohort exhibited a major complication, which was a bowel injury that was identified and corrected intraoperatively without any further complications. Minor complications were encountered in 11.4% *vs.* 8.8% of the patients. Six patients (8.8%) from the younger patient cohort exhibited minor complications, which were urinary leakage four patients, treated by leaving the catheter in place for an additional seven days; two cases of urinary retention, which was treated by inserting a new catheter and removing it two days later, and one patient with an asymptomatic lymphocele which was treated conservatively. Pelvic lymph node dissection was performed in 1623 patients (81.2%) of the overall cohort, out of which in 64 (3.2%) cases were found to be disease-positive. In the younger patient cohort, pelvic lymph node dissection was performed in 52

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

Parameters	Overall patient cohort	Patients $\leq 50$ years of age	<i>p</i> -Values
Patients	2000	68	
Age in years	63 (38-79)	48 (38-50)	0.05
Body Mass Index (BMI)	26.7 kg/m <sup>2</sup> (19-51 kg/m <sup>2</sup> )	26.8 kg/m <sup>2</sup> (21-32 kg/m <sup>2</sup> )	
Prostate size	56.1 g (10-170 g)	31.4 g (26-149)	0.05
Prostate specific antigen	10.3 ng/ml (0.3-220 ng/ml)	8.3 ng/ml (1.2-51.3 ng/ml)	
Neurovascular bundle preservation	65.7%	92.6%	0.05
Blood loss	160 ml (60-1500 ml)	144 ml (50-350 ml)	
Minor complications	11.4%	8.8%	
Major complications	1.3%	1.4%	
Operative time	156 min (80-465 min)	151 min (90-330 min)	
Length of catheterisation	5.5 days (5-31 days)	5.3 days (5-12 days)	
Gleason score			
<7	42.8%	54.4%	0.05
=7	47.7%	41.2%	0.05
>7	9.5%	4.4%	0.05
Stage			
Confined disease	73.5%	78.5%	0.05
Extraprostatic extension	25.5%	21.5%	0.05
Positive margins	8.9%	5.8%	0.05
Tumor in specimen %	16.1% (1-99%)	15.2% (1-96%)	
Positive lymph nodes	3.2%	2.9%	
Continence (12 months after treatment)	92.8%	95.5%	
Potency (12 months after treatment)	66.2%	97.3%	0.001

patients (76.4%) out of which two cases (2.9%) were positive. There was no significant difference in positive lymph nodes when comparing both cohorts of patients.

From the younger patient cohort all 68 patients were preoperatively continent and the 1-year functional outcome assessment involved 46 patients (67.6%), out of whom 45 patients (97.3%) were continent, with the remaining one exhibiting only mild incontinence (defined as the requirement for 1-2 pads daily).

One patient (1.4%) was preoperatively impotent and four patients (5.8%), due to tumor status, did not undergo a NVB sparing procedure. Thus, 63 (92.6%) underwent a bilateral NVB sparing procedure. The assessment of one-year functional outcomes involved 42 patients (61.7%). When comparing both patient cohorts at 12 months, 92.8% vs. 95.5% of patients were continent and 66.2% vs. 97.3% were potent.

After a median follow-up of 17.8 (range 3-49) months, 66 patients (97.1%) were free of biochemical progression and no disease-specific mortality was evident in the cohort of patients who were  $\leq 50$  years of age.

## Discussion

PCa is distinctly uncommon in men under 50 years of age, accounting for 1% of all patients with clinically detected PCAs while this disease is exceedingly rare in children and adolescents, with only a few reported cases (5). Based on

data from 2001 to 2003, 17% of men in the USA will develop PCa in their lifetime (16). However, the risk is directly correlated with age. From birth until the age of 39, only one in 10373 men will develop PCa, compared to one in 39 in men aged 40-59, one in 14 in men aged 60-69 and one in seven in men aged  $\geq 70$  years. According to the SEER database, 0.1%, 1.3%, 6.6%, 20.8%, 41.8% and 29.3% of PCa deaths occur in men aged 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84 and  $\geq 85$  years, respectively (1).

The influence of age on the biological aggressiveness of PCa is controversial. Historically, various studies report a higher incidence of more aggressive tumors among younger patients, leading us to suggest that they would not be ideal candidates for radical prostatectomy (6-8). Later, other researchers did not find any differences in the histological characteristics of tumors when analyzed in patients of different age groups (17). Khan *et al.* (4) compared the outcomes of radical prostatectomy between 341 men aged  $\leq 50$  years and 2556 older men at a mean follow-up of 5.7 years. In that series, younger men had significantly more favourable pathological features in the radical prostatectomy specimen. Moreover, the 5-, 10- and 15-year PSM rates for men aged  $< 50$  years were 88%, 81% and 69%, respectively. These rates were similar to those of men aged 50 to 59, slightly better than those of men aged 60 to 69 and significantly better than those of men aged  $\geq 70$  years. They concluded that men diagnosed with PCa who are younger than 50 years of age and are

candidates for radical prostatectomy tend to have a greater probability of organ-confined disease and greater long-term cancer control rates than older men. Twiss *et al.* (18) compared the surgical outcomes after radical prostatectomy between men younger than 50 years and men 50 years old or older. The outcomes were compared for 66 men younger than 50 years of age *versus* 724 men who were 50 years old or older. No significant difference was found in the risk factors for PCa between both groups. They reported that the preoperative and pathological predictors of organ-confined disease and biochemical recurrence were similar in both age groups. Out of the men in the younger group compared to the older group, 93.3% *vs.* 97.1% achieved continence and 100% *vs.* 81.4% achieved erections adequate for intercourse, respectively. They concluded that radical prostatectomy could be performed with good results and low complication rates in men with localized PCa who are younger than 50 years of age. Varkarakis *et al.* (19) reported on 26 patients younger than 45 years old who underwent radical prostatectomy. The pathological examination revealed an organ-confined disease in 84.6% of patients and an extraprostatic extension in 15.4%. PSM was seen in 7.7% cases. During a mean follow-up period of 15.8 months, all patients were continent, and 13 of the 16 patients with a follow-up of 12 months or longer were potent. They concluded that the tumors these patients had were clinically significant, but of a low stage and therefore potentially curable by surgery. Smith *et al.* (20) evaluated a surgically treated cohort of men, aged 50 years or younger in order to determine whether the disease recurred more frequently among them than at those aged 51 to 69 years. The disease-free survival curves were significantly different and the age remained a significant prognostic factor. They concluded that patients who underwent radical prostatectomy and were aged 50 years or younger had a more favorable disease-free outcome compared to older men. Rouprêt *et al.* (21) analyzed the data from 110 patients 50 years old or younger who had undergone radical prostatectomy. 39 (45.9%) by open radical prostatectomy RP and 46 (54.1%) laparoscopically. The surgical margins were positive in 12.9% of patients. The mean follow-up after radical prostatectomy was 39.1±36.8 months, time at which 10.6% patients experienced biochemical recurrence. Longer PSA-free survival after surgery was significantly associated with high-risk and intermediate-risk patients but not with the surgical procedure. They concluded that radical prostatectomy is an effective treatment of PCa in patients younger than 50 years old.

The literature lacks data on information, preferences and decision-making in young patients with PCa. Sidana *et al.* (11) evaluated 986 men under 50 years of age, diagnosed with PCa between 2001 and 2005. They discovered that the most common primary therapy was surgery in 81.4%. Freedland *et al.* (10) examined the relationship between age and biochemical failure after radical prostatectomy. They

examined the data from 1753 men treated with radical prostatectomy and compared the age, as a categorical variable, according to decade of life (50 years old or younger, 51 to 60, 61 to 70, and older than 70 years) with the clinical and pathological variables at radical prostatectomy, as well as the time to biochemical recurrence. They found that age was significantly related to the year of surgery, with the more recently treated patients being younger than less recently treated patients. They concluded that the average age of men undergoing radical prostatectomy was decreasing with time. Independently, young men have more favorable outcomes after radical prostatectomy than older men. Taken together, these findings are similar to ours and suggest that surgical treatment is warranted and likely to be associated with favourable long-term cancer control outcomes for young men diagnosed with PCa.

To our knowledge this study represents the largest separate report of RARP outcomes of patients ≤50 years of age. As seen from our results, there was a significant difference in the presence of an organ-confined disease, in extraprostatic extension, in positive surgical margins and in Gleason score. At 12 months, 92.8% *vs.* 95.5% of patients were continent and 66.2% *vs.* 93.7% ( $p<0.001$ ) were potent. After a median follow-up of 17.8 months, 97.1% were free of biochemical progression.

Although our study benefits from reporting on the largest cohort of patients ≤50 years of age analyzed so far who underwent RARP, there are two limitations that should be addressed. The first limitation is that we assessed only 1-year functional outcomes of the younger cohort patients. Out of the patients included in this analysis, only 67.6% (N=46) were included regarding continence rates, due to our inadequate follow-up period (3 to 49 months), of whom 61.7% (N=42) underwent a bilateral NVB sparing procedure. Additionally the included patients could possibly exhibit further improvement in the future, especially regarding potency rates. The second limitation is the inadequate follow-up period regarding PSA-free survival and disease-specific survival.

Despite these limitations, our findings suggest that RARP in patients ≤50 years of age is a safe surgical procedure with limited complications and excellent oncological and functional outcomes. Although the preservation of the NVB in such patients is preferable, this can be performed without compromising the radical nature of cancer surgery.

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