

Does seminal vesicle-sparing robotic radical prostatectomy influence postoperative prostate-specific antigen measured with an ultrasensitive immunoassay?

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Summary

PURPOSE: Sparing of the seminal vesicles during robotic radical prostatectomy (SVRP) is an attempt to reduce potential damage to the hypogastric pelvic nerves. However, the seminal vesicles are known to express prostate-specific antigen (PSA) and it is unknown whether SVRP influences oncological outcome measured with ultrasensitive PSA immunoassays. In a retrospective study we analysed whether SVRP affects oncological outcome in terms of ultrasensitive PSA nadir and biochemical recurrence as compared with standard robotic assisted laparoscopic radical prostatectomy (sRALP).

METHODS: Overall, 102 patients underwent robotic prostatectomy. Patients were non-randomly allocated to the following surgical techniques: a SVRP group of 39 patients who underwent robotic radical prostatectomy sparing the tips of the seminal vesicles; a standard group of 63 patients who were treated with sRALP. Inclusion criteria were histologically proven negative margins (R0) and negative lymph node status (pN0). PSA was measured with an ultrasensitive assay. The Mann-Whitney U-test was used to compare the differences in PSA nadir and follow-up PSA. Biochemical recurrence was diagnosed if PSA rose to ≥ 0.2 mg/ml.

RESULTS: Median (range) follow-up was 31.4 (16.4–43.8) months. Preoperative PSA was 5.8 (0.13–15.29) ng/ml in the SVRP group and 7.1 (0.8–46) ng/ml in the sRALP group. Two cases of biochemical recurrence occurred in the sRALP group during follow-up. One of these two patients presented with locally advanced prostate carcinoma diagnosed from the definitive pathological specimen (pT3b). No patient of the SVRP group had seminal vesicle invasion or biochemical recurrence. No significant between-group difference in terms of PSA nadir and follow-up PSA was recorded. However, the percentage of patients who did not reach PSA nadir values of < 0.01 ng/ml was higher in the SVRP group (10 vs 5% in the sRALP group).

CONCLUSIONS: Compared with sRALP, SVRP had no clinical impact on oncological outcome in terms of PSA nadir or biochemical recurrence measured with an ultrasensitive PSA immunoassay. A slightly higher PSA nadir after SVRP seems to be expected, which needs to be mentioned during follow-up of these patients.

Keywords: prostate cancer, radical prostatectomy, seminal vesicles, ultrasensitive PSA

Introduction

The common use of prostate-specific antigen (PSA) testing has led to more diagnoses of well-differentiated and organ-confined prostate cancer foci with a low risk for further systemic spread [1]. Because prostate cancer treatment such as surgery or radiation therapy is highly effective, these forms of localised prostate cancer are associated with favourable oncological control [2–4]. However, surgical treatment is associated with incontinence and erectile dysfunction in up to 35% or 66% of patients, depending on whether a nerve sparing technique has been applied [5, 6]. Moreover, the quality of nerve sparing varies among surgeons and across cases [7]. Functional outcome is further influenced by surgical application of traction or thermal energy to the inferior hypogastric pelvic plexus situated in proximity to the tip of the seminal vesicles [8, 9]. Thus, erectile dysfunction may result, even if nerve sparing has been performed. In an attempt to reduce the risk of affecting the pelvic plexus anatomy, several risk-adapted treatment strategies have been proposed, such as seminal vesicle-sparing radical prostatectomy (SVRP) [10] and, recently, even partial prostatectomy [11]. Observational studies have corroborated the improved functional outcome after SVRP [12–14] and, similarly, better functional results have been reported in patients after seminal vesicle-sparing cystectomy [15]. John and Hauri reported improved rates of urinary continence in patients undergoing SVRP compared with standard radical prostatectomy (58 vs 18% after 6 weeks, $p = 0.004$, and 95 vs 82% after 6 months, $p = 0.05$) [10]. Bellina et al. also described better early postoperative urinary continence rates after a sem-

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inal vesicle-sparing technique (95 vs 28% after 1 month) as well as improved erectile function (90% in the seminal vesicle-sparing group versus 62% in the standard group maintained the ability to achieve orgasm) [12]. Another group reported significantly higher urinary continence rates 4 weeks and 12 months postoperatively in a seminal vesicle-sparing series versus a standard group [13]. Therefore, SVRP results in improved continence.

Importantly, the epithelial cells of the remaining seminal vesicle tips have been reported to express PSA [16], which might lead to further oncological treatment on the assumption of oncological failure. Previous studies showed no significant differences in postoperative serum PSA values after SVRP [16]. The PSA assays used at that time had detection limits of 0.04 ng/ml and possibly were not able to detect the potential small amounts of PSA expressed by the remaining seminal vesicle tissue in SVRP patients. In recent years, nadir PSA measured with an ultrasensitive assay for early detection of biochemical recurrence after radical prostatectomy has increasingly been used in daily practice [17–22]. To our knowledge, the effect of the remaining seminal vesicles on postoperative PSA nadir measured with an ultrasensitive PSA immunoassay has not yet been determined. To address this, we investigated whether robotic SVRP affects oncological outcome in terms of PSA nadir and biochemical recurrence detected with an ultrasensitive PSA immunoassay as compared with standard robotic assisted laparoscopic prostatectomy (sRALP), which could lead to further investigations and therefore has clinical impact during follow-up of these patients.

Patients and methods

This study was approved by the local ethics review committee (Cantonal Ethical Review Committee of Zurich, Switzerland; KEK-ZH-Nr. 2015-0458). Informed consent was obtained from all individual participants included in the study.

From December 2013 to December 2015 we included data in the context of a retrospective study from a total of 102 patients diagnosed with prostate cancer who underwent robotic prostatectomy. Patients were stratified according to their oncological risk profile Group 1, termed the sRALP group (n = 63) consisted of patients with higher oncological risk. These patients had higher preoperative PSA values (median PSA 7.1 ng/ml), had a higher clinical T stage (cT3 in four patients, 6.5%) and were older at diagnosis (median age 69 years). These patients underwent sRALP.

All patients except three from group 2 had preoperative PSA <10 ng/ml and underwent SVRP (SVRP group, n = 39). These three patients had PSA values of 10.2, 10.3 and 15.3 ng/ml, respectively. Because of the localisation and extent of the tumour in preoperative evaluation (magnetic resonance imaging [MRI] / biopsy findings), SVRP was a suitable approach for these patients, and they were treated with the seminal vesicle-sparing approach (SVRP). Only cases with histologically proven negative margins (R0) and negative lymph node status (pN0) were included in the current analysis to ensure that postoperative serum PSA was not contaminated by remaining prostate cancer cells. None of the patients had neoadjuvant treatment. We analysed postoperative serum PSA nadir and biochemical

recurrence during follow-up as the primary endpoint of the study.

Surgical technique

sRALP (group 1)

After creating a pneumoperitoneum under general anaesthesia, five ports were inserted (two 12 mm, two 8 mm and one 5mm) and the patient was brought in a 25° Trendelenburg position. After pelvic lymph node dissection, the bladder was intraperitonealised and the bladder neck was opened. The seminal vesicles were not spared, but dissected completely. Patients of the high risk group underwent extended pelvic lymphadenectomy.

SVRP (group 2)

For SVRP a standardised technique, as described previously [10], was used. Preparation up to opening of the bladder neck was identical to that used in the sRALP group. The seminal vesicles were then gently prepared. Traction and thermal energy was avoided. The distal parts (seminal vesicle tips) were left *in situ* with a safety margin of at least 1 cm from the prostate base. Importantly, the tip of the seminal vesicles were not mobilised. Patients from group 2 underwent limited pelvic lymphadenectomy.

The technique of nerve sparing was uniform across all patients.

One experienced urologist (HJ) performed all 102 prostatectomies at the Cantonal Hospital Winterthur using the da Vinci® SI Surgical System.

Ultrasensitive PSA test and biochemical recurrence

PSA levels were measured with an ultrasensitive immunoassay that had a lower detection limit of 0.008 ng/ml (Abbott Diagnostics, Architect i1000sr®, Illinois, USA) at our clinic. PSA was tested 6 weeks and 3 months after surgery and then semi-annually thereafter. From the second year onwards, PSA was tested annually. At every visit, a physical examination including digital rectal examination for detection of local recurrence was performed. Biochemical recurrence was diagnosed if PSA rose to levels ≥ 0.2 ng/ml. We analysed PSA values at two-points in the postoperative timeline. First we compared PSA nadir levels, which are usually reached at 6 weeks after radical prostatectomy, between the two groups. Secondly, we determined whether PSA levels of the groups showed significant differences or if biochemical recurrence occurred at the time of the last recorded follow-up consultation, which was up to 43.8 months after surgery.

Statistics

Categorical data were compared with chi-square tests. Continuously coded variables were given with median and range. Continuously coded data was compared with the Mann-Whitney-U-test. IBM SPSS Statistics version 24.0 was used. All tests were two-sided with a significance level set at 0.05.

Table 1: Clinical and pathological characteristics of the 102 patients.

Patient characteristics	Group 1 (sRALP) (n = 63)	Group 2 (SVRP) (n = 39)	p-value
Age in years	69 (44–81.5)	63 (46.5–75)	0.001
Preoperative PSA in ng/ml	7.1 (0.8–46)	5.8 (0.13–15.29)	0.007
Bilateral nerve sparing, n (%)	17 (27%)	39 (100%)	0.001
Unilateral nerve sparing, n (%)	4 (6.5%)	–	
Clinical tumour stage, n (%)			0.108
T2	59 (93.5%)	39 (100%)	
T3	4 (6.5%)	–	
Pathological tumour stage, n (%)			0.015
T2	51 (81%)	38 (97.5%)	
T3a	11 (17.5%)	1 (2.5%)	
T3b	1 (1.5%)	–	
Definitive Gleason score, n (%)			0.312
5+5	–	–	
5+4	1 (1.5%)	–	
4+5	–	–	
5+3	–	1 (2.5%)	
3+5	1 (1.5%)	–	
4+4	4 (6.5%)	–	
4+3	13 (20.5%)	1 (2.5%)	
3+4	33 (52.5%)	28 (72%)	
3+3	11 (17.5%)	9 (23%)	
Definitive Gleason score sum	7 (6–9)	7 (6)	
Surgical margin status R0, n (%)	63 (100%)	39 (100%)	
Weight prostate specimen in g	54.3 (27.2–114.0)	42.9 (18–101)	0.001
Largest tumour diameter in histological specimen in mm	18 (3.0–40.0)	8.0 (1.5–25.0)	0.001
Lymph node count, n	16 (1–33)	11 (2–29)	0.003
Lymphovascular infiltration	–	–	–

PSA = prostate-specific antigen; sRALP = standard robotic assisted laparoscopic radical prostatectomy; SVRP = seminal vesicle-sparing radical prostatectomy. Data are presented as median (range) or frequency (percentage).

Results

Clinical and pathological characteristics

Table 1 depicts the patient characteristics. Median (range) follow-up duration was 31.4 (16.4–43.8) months. The two groups consisted of a high-risk group (group 1, n = 63) and a low-risk group (group 2, n = 39). Patients from group 1 underwent sRALP with extended pelvic lymphadenectomy whereas those from group 2 underwent SVRP with limited pelvic lymphadenectomy. Median age, prostate specimen weight, largest tumour diameter in specimen, preoperative PSA, pathological tumour stage and lymph node count from the pelvic lymphadenectomy were significantly higher in group 1, reflecting their higher oncological risk of systemic disease. One locally advanced prostate cancer was detected in a definitive pathological specimen in the high-risk group (pT3b). Clinical tumour stage and definitive Gleason score were comparable between the groups. None of the definitive pathological specimens showed lymphovascular infiltration.

Oncological follow-up

There was no significant difference between the two groups in terms of PSA nadir and biochemical recurrence during follow-up (table 2). Overall median time to ultrasensitive PSA nadir was 51.5 (25–993) days. Median time to ultrasensitive PSA nadir was 50 (25–382) days in group 1 (sRALP) and 55 (40–993) days in group 2 (SVRP). Median PSA nadir was 0.01 (0.01–0.02) ng/ml in group 1 and 0.01 (0.01–0.03) ng/ml in group 2 (p = 0.268). Three pa-

tients (5%) in group 1 did not reach a PSA nadir <0.01 ng/ml compared with four (10%) in group 2 (p = 0.3). The highest PSA nadirs were 0.02 ng/ml (group 1) and 0.03 ng/ml (group 2). None of these patients who did not reach a PSA nadir <0.01 ng/ml developed a biochemical recurrence up to the time of the last recorded follow-up consultation. Median time to this point was 31.4 (16.4–43.8) months. Median PSA values at the time of the last recorded follow-up consultation were 0.01 (0.01–0.53) ng/ml in group 1 (sRALP) and 0.01 (0.0–0.15) ng/ml in group 2 (SVRP) (p = 0.699).

However, two patients from the sRALP group developed biochemical recurrence (0.23 ng/ml and 0.53 ng/ml) during follow-up and therefore underwent salvage radiotherapy. One of these two patients had locally advanced prostate cancer with seminal vesicle invasion (pT3b). The highest PSA value during follow-up among patients in group 2 was 0.15 ng/ml, not exceeding the biochemical recurrence threshold of 0.2 ng/ml.

Table 2: Oncological outcome after standard robotic assisted laparoscopic radical prostatectomy (sRALP) compared with seminal vesicle-sparing radical prostatectomy (SVRP).

	sRALP (n = 63)	SVRP (n = 39)	p-value
PSA nadir in ng/ml	0.01 (0.01–0.02)	0.01 (0.01–0.03)	0.268
Follow-up PSA in ng/ml	0.01 (0.01–0.53)	0.01 (0.01–0.15)	0.699

PSA = prostate-specific antigen. Data are presented as median (range).

Discussion

In the current study, SVRP did not negatively impact oncological outcome in terms of ultrasensitive PSA nadir and biochemical recurrence as compared to sRALP. Of note, the percentage of patients who did not reach PSA nadir values <0.01 ng/ml was higher in the SVRP group. Although statistical analysis showed no significant difference, these findings most likely reflect the natural expression of the residual seminal vesicle tips since glandular epithelium cells have been shown to produce PSA [16]. Importantly, there was no significant difference between the two groups in terms of PSA nadir and follow-up PSA values. Nevertheless, this finding needs to be kept in mind during follow-up visits of patients after SVRP since PSA nadir levels above the detection limit of the ultrasensitive immunoassay used can lead to concern about prostate cancer cells left behind in the first place.

In our department, nerve sparing is performed using the intrafascial approach. This can leave residual benign prostate tissue. Moreover, the surgical urethral length during apical dissection might also result in residual benign prostatic tissue and might therefore influence the PSA course after surgery. The further course of PSA has to be awaited.

Overall, the SVRP group experienced a favourable oncological outcome in terms of postoperative PSA. Moreover, cancer control rates in terms of invasion of seminal vesicles was not compromised by the surgical procedures chosen for SVRP patients. Our results are consistent with prior reports suggesting that sparing the seminal vesicles is not associated with impaired pathological findings.

If prostate cancer invades the seminal vesicles, it usually extends mainly into the proximal proportion and rarely involves the tip [23]. In our department the technique sparing the seminal vesicle tips has been implemented in order to preserve the transverse pelvic nerves. Because the tips of the seminal vesicles are as close as 1 mm to the neurovascular bundles [8, 9], this leads to better early continence [10]. Since the landscape of prostate cancer screening has changed remarkably in the past, a stage shift has occurred and nowadays more localised prostate cancer is being detected in daily practice [1]. Moreover, lower rates of seminal vesicle invasion have been reported [24]. Therefore, treatment strategies have continuously evolved, and now include active surveillance [25] or focal therapy [26]. As a more risk-stratified surgical treatment for prostate cancer, even partial prostatectomy has been described recently [11]. SVRP is one of these evolved surgical treatment options and seems to be a safe operative technique in selected patients with appropriate prostate cancer features.

There are several studies on the functional outcome of SVRP [10, 12–15, 27, 28] and even one recent randomised controlled trial [29]. Gilbert et al. did not find a significant difference between nerve sparing prostatectomy augmented with seminal vesicle sparing and standard nerve sparing prostatectomy in terms of recovery of continence and erectile function among 140 men during a follow-up of 12 months [29]. Functional outcome was assessed by multidimensional patient reported outcomes. In contrast, the group of Studer and co-workers reported a high probability of preserving potency among men who underwent seminal vesicle-preserving and nerve-sparing cystoprostatectomy

[27]. Better early functional recovery was also observed by Albers et al. when performing perineal prostatectomy [28]. Importantly, Mogorovich et al. found a higher rate of painful orgasm among patients after SVRP [30]. Altogether, the books on the functional impact of preserving the seminal vesicles are not closed yet and further studies should clarify the impact on preserving them during surgery on the bladder or prostate.

Surgeons performing SVRP have to be familiar with the three different patterns of seminal vesicle invasion [31]. Types I and II are invasive patterns “per continuitatem” from the prostate into the seminal vesicle; type I is characterised by a direct invasion of prostate cancer cells into the seminal vesicles by spread along the ejaculatory duct system, whereas type II is extraprostatic, spreading through the capsule into the seminal vesicles. In contrast, type III is an isolated discontinuous skip metastasis. Types I and II are clinically seen often in cases of seminal vesicle invasion, whereas the type III pattern seems to occur rarely [23]. There are reports indicating that invasion of the distal centimetre of seminal vesicles is rarely seen [32]. Villers et al. detected one case out of 243 prostatectomy specimens with discontinuous involvement of the seminal vesicles [33]. In a series of 773 consecutive radical prostatectomy specimens with complete sampling of both seminal vesicles, one case with tumour involvement in the distal seminal vesicles in absence of invasion of the proximal or mid parts was described [34]. In this case, extensive lymphovascular infiltration of the tumour in the prostate gland was seen. In our series, no definitive pathological specimen had lymphovascular infiltration. This finding might be influenced by the negative pathological lymph node status (pN0), which was an inclusion criteria for the current study. However, extensive lymphovascular infiltration with skip metastases into the distal seminal vesicle seems to be a rare condition.

There are several limitations in the current study that deserve mention: first, our follow-up time is short from an oncological point of view; second, we have a small sample size; and third, this retrospective study provided results from a single institution and was not randomised [29]. Additionally, our groups were restricted to pN0R0 status in order to rule out postoperative contamination of the PSA nadir. Therefore, our results may not be directly translatable to other populations with different cancer characteristics. Furthermore, three patients with preoperative PSA values >10 ng/ml were included in the SVRP group. These patients theoretically have a higher oncological risk in terms of a future relapse of the disease. However, none of these patients showed biochemical recurrence during follow-up. On the other hand it needs to be mentioned that a few cases in the SVRP group could have been managed equally well by means of active surveillance. Importantly, some individual patients undergo radical prostatectomy because of their personal preference although they were given comprehensive information about different treatment options suitable to their individual risk. Therefore, our series does not imply that SVRP should be a surrogate to an active surveillance strategy. Further long-term investigations in a prospective manner in order to build comparable groups and/or improve the risk stratification are needed. In addition, we are aware that without addressing the

functional outcome, an overarching statement on the seminal vesicle-sparing technique is incomplete. However, in this study we were deliberately focusing on postoperative PSA. The functional outcome will be the subject of ongoing studies with larger cohorts. Urinary continence, erectile dysfunction and painful orgasm after SVRP, which seems to be a possible concern, will be specially assessed [30]. Taken together, from an oncological point of view, SVRP is a safe surgical treatment in selected patients with appropriate prostate cancer features. The anatomical background for SVRP has been described by several studies underlining the course of the pelvic (para)sympathetic nerve fibres in remarkable proximity to the tips of the seminal vesicles [9, 35, 36]. Nevertheless, some studies have shown that most nerves are situated on the lateral aspect of the seminal vesicles [37], which is why careful dissection (especially on the lateral aspect) and removal of the whole seminal vesicle is performed by some authors.

In conclusion, oncological follow-up in terms of postoperative PSA among patients undergoing SVRP was not significantly different as compared with men undergoing sRALP. The finding of slightly elevated PSA values needs to be kept in mind during follow-up visits of patients after SVRP.

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Potential competing interests

No potential conflict of interest relevant to this article was reported.

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