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TITLE PAGE

Title: NERVE SPARING IN SALVAGE ROBOTIC ASSISTED PROSTATECTOMY: SURGICAL TECHNIQUE, ONCOLOGIC AND FUNCTIONAL OUTCOMES AT A SINGLE HIGH-VOLUME INSTITUTION.

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Salvage robotic-assisted prostatectomy; nerve-sparing; neurovascular bundle; surgical technique; erectile function; continence.

MANUSCRIPT

Introduction

Prostate cancer (PC) is the most prevalent visceral malignancy in U.S. men [1]. According to the data of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry, 27.9% of men select primary non-surgical local treatments [2]. It has been shown that up to 72% of patients with increasing PSA after radiation will have locally recurrent disease. [3-5]. Recently it has been shown that 92% of men with biochemical recurrence (BCR) after radiation will receive systemic ADT while only 2% will receive potentially curative salvage radical prostatectomy (SRP) [6]. In patients with localized recurrent PC, a 48% biochemical recurrence-free survival rate and a metastasis-free survival of 83% at 5 years after SRP have been documented in a large multi-institutional study [7]. Despite this proportion of cancer control, few patients choose this therapy because historically a high complication rate and poor functional outcomes have been associated with open SRP. The loss of dissection planes as a result of ionizing radiation or other previous treatments make SRP a very technically challenging procedure. While these operative complications have decreased in more recent reports, functional outcomes continue to be a major concern [8] since high rates of urinary incontinence (up to 67%) and erectile dysfunction in virtually all patients have been described in the literature [9-11].

Recently, salvage robot-assisted radical prostatectomy (sRARP) has emerged as an alternative to the open approach for these patients. These series are relatively small and the follow up is limited. However, these studies suggest that sRARP is a feasible treatment option for qualified patients with recurrent prostate cancer after primary therapy with equivalent oncologic outcomes and less convalescence than the open approach. Complication rates seem to be better in sRARP series but functional outcomes are minimally assessed in the literature [12-17]. Besides, few of these studies reported performing NVB preservation during sRARP because of the altered pelvic anatomy and loss of tissue planes.

The primary objective of the present study is to analyze the feasibility of NVB preservation during sRARP and evaluate its impact in functional outcomes, especially on the recovery of erectile function. The secondary objective is to assess the oncologic outcomes in this setting.

Patients and Methods

Patient population and data collection

After Institutional Review Board approval, between January 2008 and March 2016, a total of 6654 consecutive patients underwent Robot-assisted Radical Prostatectomy (RARP) for localized PC by one single surgeon (V.P) who had prior experience with >2000 RARP procedures. Among those patients, 80 underwent sRARP due to a local recurrence after primary treatment, either radiation (63) or ablative treatments (17). All of them had a confirmation positive biopsy and negative computed tomography and bone scan. The quality of NVB was graded by the surgeon prospectively at the termination of the sRARP using a 1-5 scoring system (1 = 0%, 2 <50%, 3 = 50%, 4 = 75% and 5 ≥95%) as described previously [18]. The overall NVB preservation was obtained from the mean of both side's percentages. To perform the descriptive and comparative analysis in terms of NVB preservation, these patients were categorized into two groups depending on the degree of nerve sparing (NS) performed: those patients with ≥50% overall NVB preservation were included in Good-NS (G-NS) Group (43) and those with <50% of overall NVB preservation were classified in Poor-NS (P-NS) Group (37).

Primary outcomes measure between the groups included: preoperative SHIM scores and AUA symptom scores, BMI, Charlson Score, PSA, primary treatment, operative time (OR), estimated blood loss (EBL), NS degree and approach and complications (intraoperative and postoperative). All data variables were collected and entered in a prospective fashion. Morbidity was reported using Clavien-Dindo Classification.

Oncologic results were reported using biochemical failure (BCF), comprising BCR (defined by 2 consecutives PSA values >0.2ng/ml and rising) and PSA-persistence (defined as PSA values >0.2ng/ml at 6 weeks after sRARP). Functional results were collected by clinical assessment or by telephone interview and reported as follows: potency was defined as the ability to achieve a successful erection with penetration over 50% of the time (with or without the use of oral phosphodisterase 5 (PDE5) inhibitors). Patients having intercourse dependent only on penile injection, vaccum erection device (VED) or transurethral alprostadil were not considered potent.

Full continence was defined as 0 pad/day and 0-2pads continence as ≤2 pads/day. Follow-up information was entered in the database at 6 weeks, 3, 6, 9, 12, 18-months and at 1 year intervals.

Surgical technique – TIPS AND TRICKS OF NERVE-SPARING IN sRARP

All procedures were transperitoneal and used the six-port technique with the DaVinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). A pelvic lymph node dissection was performed in all the patients during sRARP.

The RARP and sRARP steps are similar, however some precautions need to be taken to minimize morbidity, especially in the steps described previously by our group [19]. Regarding the NS technique, we give the details of some specific tips we are using to maximize functional results.

1. Anterograde or Retrograde approach?

   Both can be used in SRARP, depending on the experience and preferences of the Surgeon. But in those patients with a severe grade of adhesions and fibrotic tissue, anterograde approach is preferred to have better visualization and control of the structures, maximizing safety and functional outcomes.

2. Endopelvic Fascia (EPF) Dissection

   Secondary adhesion and vessel injury are common in this setting, mostly after radiation treatments, and may result in loss planes or troublesome bleeding during EPF dissection and NVB injury in a very early step of sRARP (Figure 1A). Hence, immediate hemostasis is necessary as soon as bleeding is encountered to facilitate further visualization of NVB. This step is particularly difficult in patients who underwent proton beam radiation treatment (PBRT).

3. Posterior dissection (Instant Toggling):

   Unlike non-salvage procedures, the correct plane in posterior dissection can be difficult to identify due to the fact that this tissue is usually replaced by fibrotic layers. Thus, when using retrograde NS approach, this step should be done gently with the back of scissors with no thermal energy and sharp dissection should be reserved for only when resistant fibrotic adhesions are encountered.

At this point we use the instant toggling of the camera to get a better visualization of the posterior plane and improve the NVB preservation during its medial approach.

4. Lateral NVB dissection:

In very few cases, the NVB dissection is easy and does not differ so much from standard RARP. However, most of the times the correct plane is difficult to find due to the adhesion of the structures (Fig. 1B) or the abnormal vascularization (Fig. 1C) after the primary treatment, so it's really important to perform a blunt NVB dissection to preserve the nerves.

In the most difficult cases, a severe fibrosis can be seen during the NVB dissection (Fig. 1D). In this cases it's necessary to use sharp dissection and it's very difficult to perform a full nerve-sparing.

5. Apical NVB dissection

In salvage setting, it's essential to firmly ligate the DVC before division to avoid back bleeding, facilitate the apical dissection and section of the urethra and to obtain the maximum length of urethra to facilitate the anastomosis and improve continence. The apical NVB runs parallel at this point, so it's important to perform a gentle dissection avoiding an excessive use of the thermal energy, to preserve the distal fibers of the NVB (Fig. 1E). We found this step especially difficult in patients who underwent brachytherapy.

When a full NS is possible in sRARP, the final view of NVB is very similar from the standard RARP procedure. (Fig. 1F).

Statistical analysis

Categorical data was reported as counts and percentages. Normal distributed continuous variables were expressed as the mean and standard deviation and median and interquartile range was used in Non-normal distributed continuous variables.

Two-sample t-tests were used to test the equality of means in normal continuous variables, Mann Whitney U test in non-normal continuous variable and the chi-squared test was used in categorical data analysis. Kaplan–Meier method and regression models were used to identify survival estimations and predictors of potency, continence and biochemical failure. Values of $p < 0.05$ were considered statistically significant. SPSS software ver. 22.0 (SPSS Inc., Chicago, IL) was used to perform the statistical analysis.

Results

Preoperative and demographic data

Preoperative, clinical and demographic data comparisons between the G-NS Group (n=43) and the P-NS Group (n=37) are summarized in supplementary table 1.

Mean age, BMI and Charlson Score did not differ between them ($p>0.05$) while preoperative PSA was slightly higher but not significant in the P-NS group ($p=0.054$). A slightly higher proportion of patients primarily treated by radiation were seen in G-NS Group (86% Vs 70.3%, p=0.085) as well as a lower time from primary treatment (52.4 ± 47.9 Vs 75.68 ± 48.6 months, p=0.050). No differences in previously potent patients (SHIM ≥ 20) were observed between the G-NS Group and the P-NS Group (32.6% Vs 29.2%; p=0.786) and all patients in both group were continent before surgery.

Intraoperative and postoperative data

There were no differences in estimated blood loss (EBL), total operative and console time between groups (p>0.05) as shown in sup. table 2. As by design, a higher overall degree of NS was observed in the G-NS Group (66.4% Vs 20.1%; p<0.001) and the most frequent access was the retrograde approach. There were no intraoperative complications and the overall incidence of postoperative complications was low in both the G-NS Group (2.3%) and the P-NS Group (8.1%) with no statistical differences between them (p=0.237). All of them were minor complications according to Clavien-Dindo Classification (1 urinary tract infection and 3 Lymphoceles with no drainage requirement). Radiological anastomotic leaks did not differ either between groups (25.6% in G-NS Vs 35.1% in P-NS Group; p=0.353) and they were successfully managed with prolonged catheterization. A cystogram was performed every 7 days to confirm the healing of the anastomoses before catheter removal. No differences were observed in the length of hospital stay between groups, however the P-NS Group required the catheter slightly longer compared to G-NS (15.0 ± 10.8 days Vs 11.95 ± 7.8 days; p=0.147).

Pathological and Oncological data

As sup. table 3 reflects, smaller tumors (1.4 ± 0.6 cm Vs 1.7 ± 0.6 cm; p=0.074) and lower volumes (14.8% ± 12.4 Vs 21.3% ± 14.4; p=0.037) were observed in the G-NS group compared to the P-NS Group. A slightly higher proportion of locally advanced prostate cancer (≥ pT3a) was observed in the P-NS Group (62.2%) compared to the G-NS group (44.2%) (p=0.108). There were no differences of positive surgical margins (PSM) between groups (14.3% in G-NS group versus 25% in P-Ns group; p=0.231) and most of them were found in the apex in both groups (66% and 44% respectively). No differences were found in terms of post-operative PSA (p=0.612), ADT need after sRARP (18.6% and 10.8%, p=0.330) or BCF at 12 months between groups (26.1% and 29% respectively, p = 0.801). The estimated BCF-free rate at 36 months were 69 and 66% respectively (p = 0.809) (Fig 2). In multivariate analysis, including NS, only Gleason score 8-10 was predictive for BCF (p = 0.009) (sup.Table 4).

Functional data

Potency and continence rates in each interval of follow-up are shown in table 1 for both groups. Potency rates were higher in the G-NS Group in all intervals compared to the P-NS Group (p>0.05). Potency at 12 months returned in 25.6% of patients in the G-NS Group and 4.3% of the P-NS Group (p=0.036). In multivariate analysis, while Good NS tended to be predictive of potency at 12 months, almost reaching significance (p = 0.065), there were no differences when comparing primary treatment received (Radiation Vs Ablative –Cryo/HIFU) (p=0.699) (sup. Table 5). The cumulative incidence curve reporting the proportion of postoperative potent patients showed a trend to be higher and faster in the G-NS group compared to the P-NS Group (p=0.086) (Fig. 3).

While full continence rates were slightly, but not significantly, higher in the G-NS Group compared to the P-NS Group in all periods of follow up (p>0.05), similar 0-2pads continence rates (77.4% Vs 78.3, p=0.941) were observed in both groups at 12 months of follow up. A similar timing and proportion of patients achieving full continence between groups was observed through the time (P=0.955) (Sup Fig. 1). In multivariate analysis, a Good NS tended to predict continence at 12 months (p = 0.119) but only non radiation – primary treatment was predictive of continence at 6 (p = 0.031) and 12 months (p = 0.033) (Table 3, sup. Table 5).

Discussion

Locally recurrent prostate cancer after RT or other ablative techniques can have an aggressive natural history with poor outcomes [20]. Among the different approaches to treat recurrent prostate cancer only 2% of the patients undergo salvage RP because, despite good cancer control, historically, salvage RP has been associated with significant morbidity and poor functional outcomes [9-11].

Recently, sRARP has emerged as an alternative for these patients with equivalent oncologic outcomes and less convalescence than the open approach [21], but functional outcomes continue to be a major concern and are minimally assessed in literature. Postoperative potency is gaining importance since these patients are being diagnosed at younger ages, earlier stages and with an acceptable preoperative erectile function despite the primary treatment.

Only a few studies have reported postoperative erectile function after sRARP [13, 16,22] ranging from 20 to 29% among preoperative potent patients, but none of them analyzed the impact and feasibility of NVB preservation in sRARP. To our knowledge, this is the first study describing the NS technique in this setting and the largest one reporting the recovery of potency in patients who underwent NS sRARP. Our group reported a retrospective study of 53 patients undergoing sRARP comparing potency recovery between them and a matched “non-salvage” RARP. Nerve sparing was performed in all RARP patients (33.9% full NS; 66.1% partial), however any degree of NS was not possible in 7 s-RARP patients (13.2%). A lower proportion of s-RARP patients were potent at 36 months comparing to non-salvage patients (31.5% Vs 49.4%) [23]. Masterson et al, assessed the feasibility of NVB preservation in the open salvage RP setting performing NS in 29 of 100 patients (29%). Six of 29 (20.7%) of them recovered potency after surgery and time to potency was frequently prolonged, with three of six patients recovering potency three years or more after salvage RP [24].

In our study we assessed the impact of the NVB in terms of functional outcomes after sRARP, comparing those patients who underwent >50% of NS (43) and those with less than 50% of NVB preservation (37). Among 53 patients with 12 months of follow up, 25.6% who underwent G-NS recovered potency versus only 4.3% with P-NS. As reported previously in the literature, recovery in terms of functional outcomes is longer in sRARP compared to standard RARP [12]. In our report, time to potency tended to be shorter in the NS group after sRARP. Most of these patients used PDE5 inhibitors at 12 months.

Regarding continence, Stephenson et al. [8] showed acceptable continence rates at 5 years following open SRP with 39 % of patients dry and 68 % requiring 1 pad daily or less. In a more contemporary open series, a 64.2% of full continent rate and 80% of 0-1pads rate were reported [25]. In our series, overall continence rates 12 months after sRARP were high in both groups, but no great differences were seen between them, either in terms of full continence (58.1% in G-NS Vs 47.8% in P-NS Group) or 0-2 pads continence (77.4% in G-NS Vs 78.3% in P-NS Group). The unique factor predicting better continence was the primary treatment received, giving to those patients who underwent non-radiation primary treatment a higher probability of reaching continence at 6 (64.3% Vs 30.8%) and 12 months (90% Vs 45.5%) after sRARP.

It's remarkable that no differences in terms of oncological outcomes were observed regarding NVP preservation degree, since BCF disease free survival was similar in both groups. As reported previously in the literature [22], only a high Gleason score (8-10) was predictive for BCF in our series. Contrarily to other standard RARP studies, a lower proportion of PSM was shown in those patients who underwent NVB preservation [26]. That could be explained by the lower proportion of locally advanced prostate cancer and smaller tumor volume in G-NS Group. Probably, these 2 factors most likely influenced the ease of NVB release and final overall grade of NS during the salvage procedure. Thus, an increasing proportion of patients are potential candidates for NS sRARP, provided that surgical margins and oncological outcomes are not compromised in selected patients.

Preoperatively, we select patients for NS on the basis of previous erectile function and cancer features, so we tend to offer a higher grade of NVB preservation in younger patients with good preoperative sexual function and early stages of recurrent prostate cancer. However, the ease of NVB release assessed intraoperatively was the most important factor regarding the final grade of NS in sRARP. That, from our point of view, depends on the kind of primary treatment and stage of prostate cancer being more difficult in patients who underwent radiation primary treatment, in particular PBRT, as well as those with locally advanced recurrent disease. In the rest of the settings, NS is feasible, safe and offers a hope to those patients with recurrent PC interested in the recovery of erectile function after sRARP. Concerning all these factors, it's important to remark that it's difficult to predict the NS grade and further functional outcomes before salvage surgery but it allows the surgeon to advise future patients on their likely potency outcomes when the surgeon inform the patient after sRARP. Considering all the potential selection bias factors mentioned, no differences were found concerning all of them between groups in univariate analysis nor in the multivariate analysis regarding potency, and instead, there was a clear trend predicting potency at 12 months in the multivariate analysis regarding type of NS.

Technically, the challenging parts of the salvage procedure were the posterior and the apical dissection. The planes were often significantly worse with prior Radiation therapy over ablative. The PBRT was the most destructive intermediate of lateral spread to the tissues beyond the prostate. Proton appeared to have the least focused energy and most collateral damage. "Generally, the vesicourethral anastomosis (VUA) was performed similarly to non-salvage setting, with a Van Velthoven VUA with a running suture (double needle, 2-0 Quill, 16 cm × 16 cm in length, half-circle 17-mm needle), with bladder neck reconstruction, an anterior suspension stich, and posterior reconstruction. In the last 19 patients of the cohort an urinary bladder extracellular matrix (UB-ECM) scaffold was incorporated into the posterior aspect of of the VUA to decrease the rate of anastomotic leak in sRARP [27].

Our study has some limitations that have to be addressed. First, it is a retrospective analysis of prospectively collected data and there is a potential selection bias (previously mentioned). Second, the small number of patients in both groups limits the power of statistical analysis and the strength of its conclusions. Third, the outcomes obtained in this study were seen in a high volume center with a highly experienced unique surgeon, so these results may not be generalized to a low volume center.

Fourth, the assessment of potency or continence (including validated questionnaires and open interviews) is not yet standardized, so discrepancy regarding the definition of potency before and after sRARP, together with the short follow up available in this series (given the well-known delay in recovery of potency and continence in the salvage setting), may have an effect on the functional outcomes. Fifth, any comments on oncological outcomes should be brought with caution, since one-year follow-up is too short to address strong statements in this setting.

In conclusion, to our knowledge, up to now, our study is the largest one assessing specifically potency and continence outcomes, and feasibility of NVB preservation in sRARP. Despite the relatively small number of patients, the findings of this study supports the feasibility and safety of NVB preservation in select patients in a high-volume institution and the subsequent better recovery of adequate erections for intercourse without compromising short-term oncological outcomes. These results offer hope to select patients who want a cure for a locally recurrent prostate cancer while preserving potency. The unique factor predicting continence after sRARP was the first treatment received, reaching better continence those patients who underwent ablative therapies.

Aknowledgements

None

Conflict of interest

None declared

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LEGENDS

Table 1. Functional outcomes

Table 2. Multivariate analysis predicting potency after sRARP

Table 3. Multivariate analysis predicting continence after sRARP

Figure 1. Pictures of different steps and challenging situations during NS in sRARP. A. Abnormal Bleeding during endopelvic Fascia dissection. **B.** Adhesions and neovascularization of the the Right NVB. **C.** Bleeding during left NVB dissection. **D.** Apical Blunt dissection of NVB. **E.** Final view of Full NS in sRARP after EBRT.

Figure 2. BCF-free survival after sRARP

Figure 3. Cumulative probability of potency after SRARP

Supplementary Table 1. Preoperative and Demographic data.

Supplementary Table 2. Intra and postoperative data

Supplementary Table 3. Pathological and oncological outcomes

Supplementary Table 4. Multivariate analysis predicting biochemical failure after sRARP

Supplementary Table 5. Functional Outcomes comparing primary treatment (Radiation Vs Ablative).

Supplementary Figure 1. Cumulative probability of continence after sRARP

(1)

Table 1. Functional outcomes

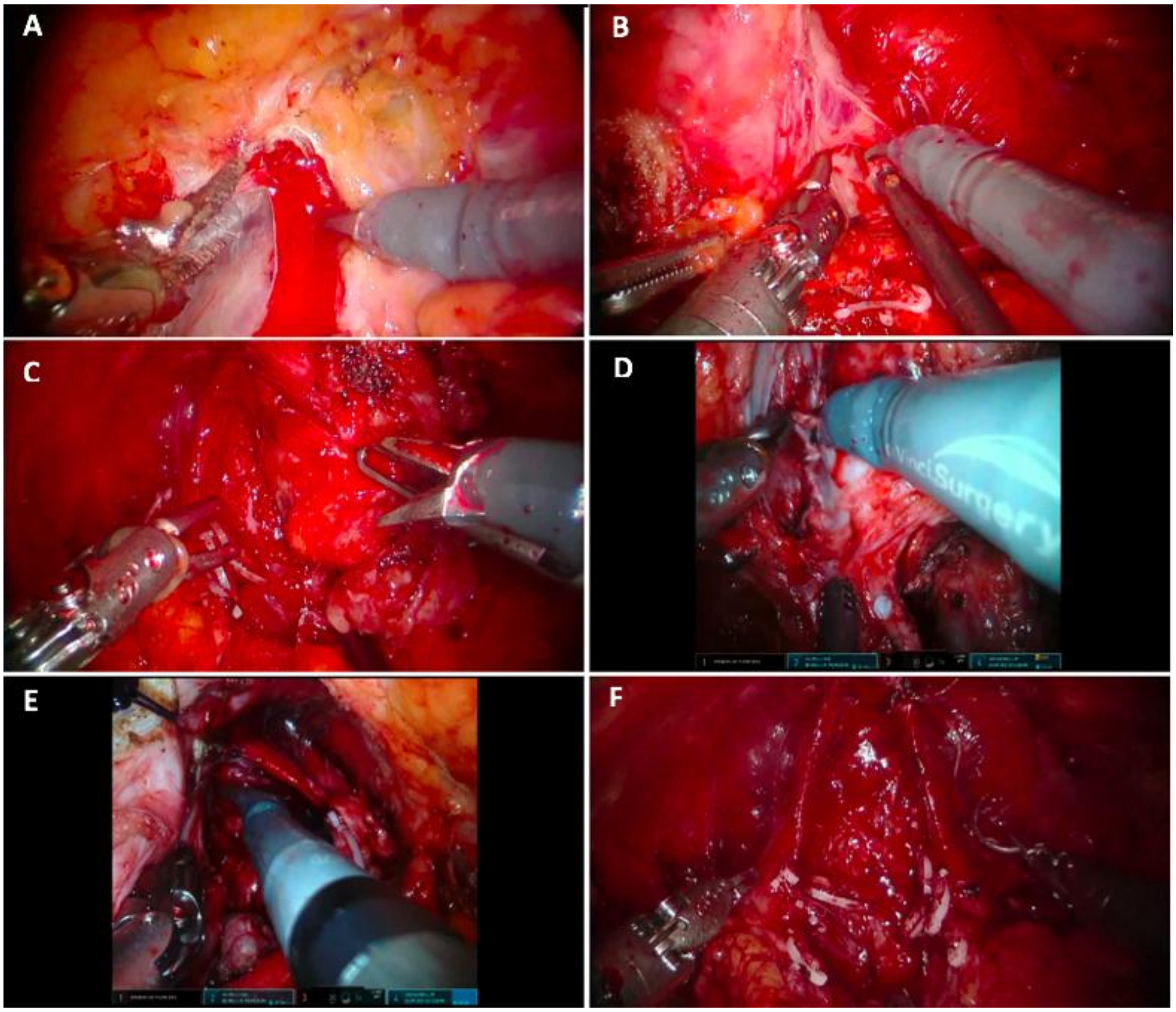
Parameters	Overall	Good NS (≥50%)	Poor NS (<50%)	Sign
Potent, n/ total (%)				
3m	7/69 (10.1%)	5/39 (12.8%)	2/30 (6.7%)	*0.401*
6m	9/66 (13.6%)	7/37 (18.9%)	2/29 (6.9%)	*0.158*
9m	8/60 (13.3%)	7/34 (20.6%)	1/26 (3.8%)	*0.059*
12m	9/54 (16.6%)	8/31 (25.6%)	1/23 (4.3%)	*0.036*
Days to potency, mean ± SD	219.3 ± 316.9	153.3 ± 178.5	417.3 ± 588.5	*0.520*
Full continent (0 pads), n / total (%)				
3m	22/69 (31.9%)	13/39 (33.3%)	9/30 (30.0%)	0.768
6m	25/66 (37.9%)	15/37 (40.5%)	10/29 (34.5%)	*0.615*
9m	28/60 (46.7%)	17/34 (50.0%)	11/26 (42.3%)	*0.554*
12m	29/54 (53.7%)	18/31 (58.1%)	11/23 (47.8%)	*0.456*
0-2 pads continence at 12 months, n (%)	42 (77.7%)	24 (77.4%)	18 (78.3%)	*0.941*
Days to continence, mean ± SD	227.9 ± 253.4	156.8 ± 183.7	301.5 ± 295.4	*0.070*
Follow-up, months, mean ± SD	22.5 ± 18.1	20.3 ± 15.5	25.08 ± 20.7	*0.251*

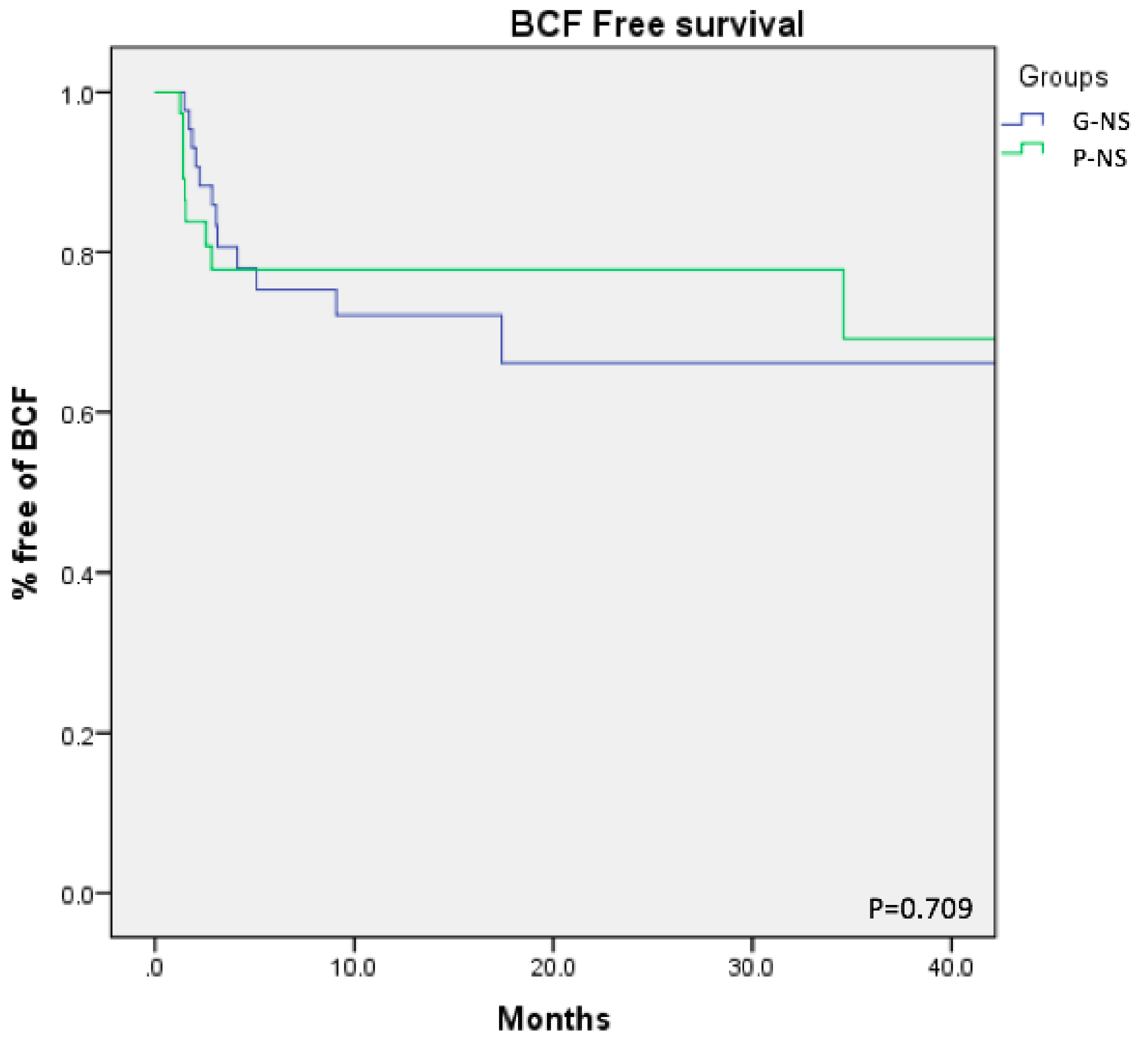
Table 2. Multivariate analysis predicting potency after sRARP

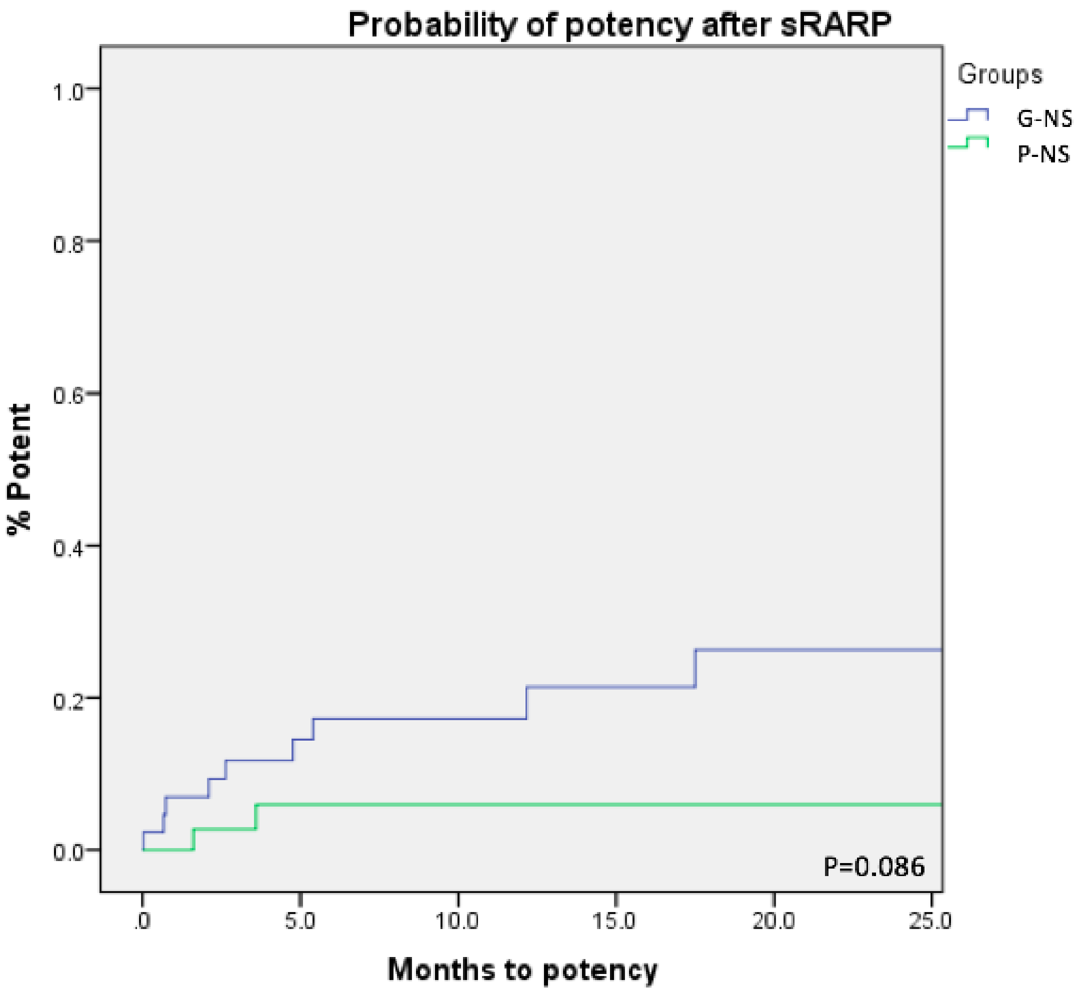
Parameters	Potency at 3 months		Potency at 6 months		Potency at 12 months	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age	0.969 (0.857 - 1.097)	*0.620*	0.943 (0.846 - 1.050)	*0.281*	0.956 (0.860 - 1.063)	*0.408*
1º Treat - Cryo/HIFU Vs RT	0 (0.000-)	*0.999*	0.273 (0.028 - 2.634)	*0.261*	0.610 (0.050 - 7.478)	*0.699*
BMI	0.863 (0.685 - 1.088)	*0.213*	0.901 (0.746 - 1.088)	*0.278*	0.957 (0.794 - 1.153)	*0.641*
Preop. potent (SHIM ≥ 21)	2.142 (0.405 - 11.323)	*0.370*	0.903 (0.174 - 4.675)	*0.903*	0.643 (0.124 - 3.336)	*0.600*
Good NS	1.162 (0.161 - 8.387)	*0.881*	1.970 (0.333 - 11.657)	*0.455*	7.652 (0.883 - 66.317)	*0.065*

Table 3. Multivariate analysis predicting continence after sRARP

Parameters	Continence at 3 months		Continence at 6 months		Continence at 12 months	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age	1.002 (0.925 – 1.086)	*0.951*	1.007 (0.928 – 1.093)	*0.861*	1.062 (0.970 – 1.164)	*0.193*
1º Treat - Cryo/HIFU vs RT	1.559 (0.442 – 5.494)	*0.490*	1.728 (0.563 – 5.308)	*0.031*	10.350 (1.204 – 88.954)	*0.033*
BMI	0.949 (0.831 – 1.065)	*0.331*	0.953 (0.835 – 1.088)	*0.478*	0.962 (0.825 – 1.121)	*0.621*
Preoperative AUA score	1.010 (0.938 – 1.084)	*0.797*	1.007 (0.935 – 1.085)	*0.857*	1.003 (0.925 – 1.088)	*0.940*
Good NS	1.153 (0.378 – 3.519)	*0.803*	1.970 (0.333 - 11.657)	*0.339*	2.900 (0.761 – 11.053)	*0.119*


A
B
C
D
E
F


BCF Free survival
% free of BCF
1.0
0.8
0.6
0.4
0.2
0.0
.0
10.0
20.0
30.0
40.0
Months
Groups
G-NS
P-NS
P=0.709


Probability of potency after sRARP
Groups
G-NS
P-NS
% Potent
1.0
0.8
0.6
0.4
0.2
0.0
.0
5.0
10.0
15.0
20.0
25.0
Months to potency
P=0.086