Image guided surgery: clinical validation of lesion identification technologies and exploration of nerve sparing approaches

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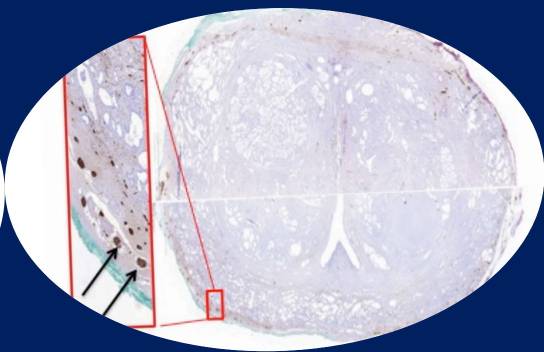
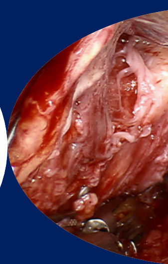
Chapter 10





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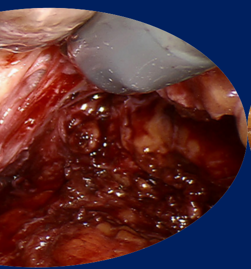
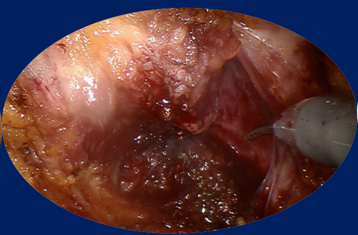
A prediction model that relates intraoperative fascia preservation to erectile dysfunction in patients that underwent nerve-sparing prostatectomy





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ABSTRACT

INTRODUCTION

Robot assisted radical prostatectomy (RARP) is performed in patients with prostate cancer. Unfortunately, 10-46% of the men who underwent RARP suffer from limited erectile function (EF). The objective for this chapter was to relate fascia preservation (FP) to EF and use these relations to develop a prediction model.

METHODS

To study the predictive value of a FP score for post-prostatectomy EF (following the international index erectile function (IIEF) score) a cohort of 1241 patients was examined. To increase the predictive value of the scoring system, the FP regions were related to postoperative IIEF, nerve distribution and co-morbidity factors. Finally, a prediction model for EF was developed based on the studied cohort.

RESULTS

Patient, tumor and surgical characteristics were registered. FP score was explored using the Phi coefficient. A multivariable linear regression model was fitted to all locations, and the importance of each region was measured by the contribution to the R2. To predict the postoperative IIEF score a logit transformed postoperative IIEF was used as the dependent variable in the regression models. When corrected for the preoperative IIEF, the FP score was shown to be significant denominator for IIEF ($p = 2.5*10^{-15}$) with an R2 of 35%. Variable selection performed using the Akaike information criterion led to a final prediction model for postoperative IIEF after nerve-preservation based on the FP score.

CONCLUSION

Quantitative nerve-sparing FP scoring could be related to the EF and integrated into a multivariate prediction model, which includes with age, use of surgical clips, the Charlson Comorbidity Index Score (CCIS), and preoperative IIEF. The retrospective design of this study and relative inaccuracy of the IIEF were considered to be limiting factors.

INTRODUCTION

Robot assisted radical prostatectomy (RARP) is frequently performed in patients with clinically localized prostate cancer. While use of a robot is said to enhance the surgical accuracy, 10-46% of the men who have undergone RARP still suffer from limited erectile function (EF) [1]. EF is thought to be directly influenced by damage induced to the periprostatic nerves that surround the prostate on the dorsolateral side (neurovascular bundle (NVB)) [1–3].

After Walsh et al.[4] identified the importance of the NVB for erectile function preservation, several nerve-preservation methods have been reported [1–3,5]. While it is not yet completely clear which nerves are most important for EF, the potential of extended nerve preservation is underlined by the fact that anatomical studies indicate that nerve structures extend into the entire circumference of the periprostatic fascia [3,4,6]. This realization has resulted - among others - in the development of the "veil of Aphrodite-approach", using the so-called high anterior release to preserve as much periprostatic fascia as possible [7]. Other approaches are bi- or unilateral nerve sparing [8–10] or the intrafascial and interfascial nerve sparing technique [2,11]. The latter was further refined into the inverse five-grade scale, as described by Patel et al. [12]. A common denominator for the intrafascial and interfascial approaches is the separation of different layers within the fascia that surrounds the prostate [11].

Currently, nerve sparing is guided by the tumor spread and the urologists ability to dissect around the delicate nerves. While desirable, intraoperative distinction between the fascia layers is technically not always feasible. To circumvent this limitation, the fascia preservation (FP) score was developed and initially evaluated in 107 patients [13]. This procedure accounts for the full circular distribution of the periprostatic nerves via a 12-tier score (Figure 1A). As the resulting ±1cm wide fascia segments can be easily assessed and documented intraoperatively, this scoring system can be applied based on tumor location and extracapsular growth. This results in a quantitative score of preserved nerves that is in optimal balance with R0 tumor resections. With such a scoring mechanism the surgical procedure can be related with patient characteristics and postoperative EF preservation, providing the basis for a much desired prediction model for the surgical outcome. The latter would help preoperative assessment of the possible value of the complex and time consuming nerve preservation approaches. In addition, a prediction model will enable the patient and urologist to jointly realize fitting care by striking a more precise consensus in the balance that should be struck between radical tumor excision and the EF. Herein EF can be considered as a measure of the patient's quality of life. In the present study the predictive value of FP score for post-prostatectomy EF was validated in an independent cohort of 1241 patients. To increase the predictive value of the scoring system the different FP regions were related to postoperative EF and nerve distribution as well as additional co-morbidity factors such as the Charlson Comorbidity Index Score (CCIS), alcohol use, smoking, use of clips, lymph node dissection (LND) and age. Finally, a prediction model for EF was developed based on the studied cohort.

METHODS

Patients and International index of erectile function – Erectile Function 5 (IIEF)

In this study 1241 patients who underwent RARP were included. The International index of erectile function – Erectile Function 5 (IIEF) was evaluated both pre- and postoperatively. Interventions were performed at the Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital. A more detailed description of the inclusion criteria and the evaluation of the IIEF score is provided in the supplemental information (SI) section.

Surgical procedure

Transperitoneal RARP procedures were performed as previously described by Menon et al. [14]. Fascia preservation was performed in an antegrade fashion, following bladder neck transection. The FP score was rated intraoperatively by assessing fascia preservation at twelve positions circumferentially (Fig 1A) using laparoscopic inspection of both the preserved fascia and the prostate surgical specimen [13]. More details considering the surgical procedure are provided in the SI.

Statistical Methods

Patient, tumor and surgical characteristics describing the population are presented descriptively in the SI (Table SI1). FP score-based patterns of the nerve sparing procedure were explored using the Phi coefficient, which is the equivalence of the Pearson correlation coefficient for binary data. A multivariable linear regression model was fitted to all locations and the importance of each of them was measured by the contribution to the R2, as described by Lindemann et al. [15].

To predict the postoperative IIEF score (range between 0 and 30) a logit transformed postoperative IIEF (logit(IIEF) = log (IIEF/30 / (1 – IIEF/30)) was used as the dependent variable in the regression models. The obtained logit transformed postoperative IIEF's were transformed back, realizing an interpretable value of the predicted IIEF. For exploratory

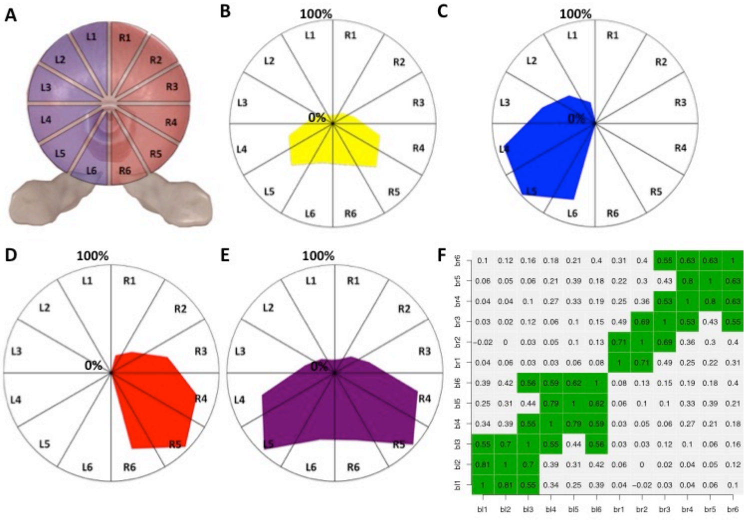

Figure 1. Surgical sparing of FP regions (n =473):

A) Schematic overview of the different FP locations (left in blue and right in red).

B) Illustration of the overall percentile distribution of the FP segments spared during surgery of the total group (FP 0 patients included, n = 1241; yellow). The pattern of FP segments spared in patients have been provided for **C)** patients that only received unilateral sparing on the left side (n= 208; blue), **D)** unilateral sparing on the right side (n =208; red), and **E)** for patients that received bilateral sparing (n = 538; purple).

F) Matrix-based correlation between the spared FP segments measured through Phi coefficient. Herein green presents a moderate or high correlation, while weak or no correlation is represented by uncolored sections.

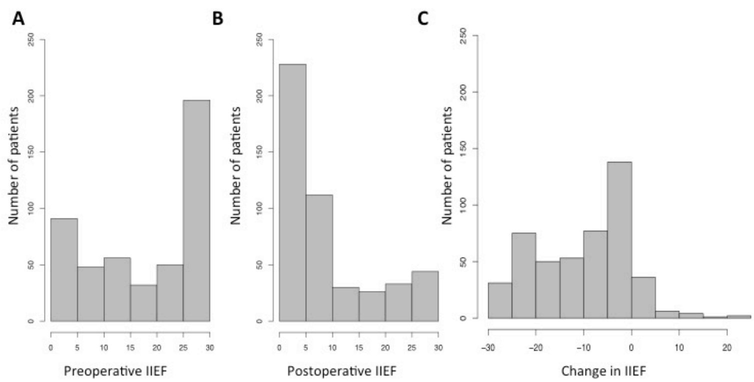

Figure 2. Pre- and postoperative frequency histograms of IIEF and change in IIEF after 12 months (n = 473):

A) preoperative IIEF scores; **B)** postoperative IIEF at 12 months; **C)** postoperative changes in IIEF.

purposes, univariable linear regression models were fitted for the individual predictors. The linearity assumption between the logit-transformed IIEF and continuous predictors was explored and, if necessary, the quadratic terms were entered. In the final multivariable model all predictors were entered, irrespective of their significance in the univariable models. Additionally, three interaction terms were added: $IIEF_{preoperative}$*FP score, $IIEF_{preoperative}$*age and FP score*age. Variable selection was performed using the Akaike information criterion (AIC). Goodness of fit was evaluated using R2 and the accuracy was evaluated visually by plotting smoothed relationship between observed and predicted scores.

RESULTS

Nerve sparing surgery

The regions and frequencies wherein fascia was spared within the specific FP regions for the total group of 1241 patients are presented in Figure 1. The median FP score was 4 (Interquartile range IQR 0-6), and 17% of patients who underwent a RARP presented an FP ≤ 6. In approximately a quarter of the patients (27%), fascia sparing was not applied (FP 0). In a mere 1% of the patients the total fascia was preserved during prostatectomy (FP 12). Intraoperatively, adjacent FP regions were often spared in combination, e.g. quadrants of the prostate circumference (Figure 1F). In the sub-population of patients that filled in the questionnaires postoperatively (n = 473; 38% of the total number of patients included) a highly similar trend was observed (Figure SI3A).

To obtain insight into the nerve distribution in the complete fascia, mid prostate stained sections of ten patients that did not receive nerve sparing surgery were analyzed (FP 0; Figure SI 1 the results were in line with previous literature (See SI for methods and results).

Correlation of postoperative IIEF and FP score

The non-parametric correlation coefficient between the IIEF score at 12 months after RARP (postoperative IIEF; Figure 2 and Table SI2) and the total FP score was 0.5 (Figure 3B). When corrected for the preoperative IIEF, the FP score was shown to be significant denominator for IIEF ($p = 2.5*10^{-15}$; Figure 3B) with an R2 of 35% (19.9% of variance explained by baseline IIEF and 15.60% of variance explained by FP). A linear regression model that included preoperative IIEF and 12 binary variables representing sparing of a particular location resulted in an R2 of 38% (adjusted R2 of 36%). Baseline IIEF contributed to 16% of variance, while the remaining 22% could be contributed to FP regions, with the highest contribution of L3, L5, L6, R3 and R4 (2.3, 3.5, 3.0, 2.6 and 2.2%, respectively).

No specific FP region could be identified as being most relevant for postoperative IIEF outcome (Figure 3C), but there seemed to be a positive influence of bilateral sparing (Figure SI3). Comparison between bilateral and unilateral sparing revealed a mean drop in IIEF of 8.8 and 11.5, respectively (Mann Whitney U test p =0.006). For a more detailed description of exact uni- or bi-lateral FP score numbers and their influence on the IIEF, see the SI.

Prediction model

Age, CCIS, smoking, alcohol intake, preoperative IIEF score, FP score, use of clips and lymph node dissection were considered potentially predictive for the postoperative IIEF (Table 1). Univariable linear regression showed that all covariates, apart from alcohol intake and smoking, were significantly associated with postoperative IIEF. The relationship between logit(IIEF) and preoperative IIEF was nonlinear, hence the added quadratic effect for this predictor. Variable selection done using the AIC led to the following prediction model:

$$\mathbf{y = logit(IIEF) = 1.95 - 0.0168 * IIEF_{preoperative} + 0.0017 * IIEF_{preoperative}\ 2 - 0.0671 * age + 0.0021 * FP + 0.3651 * clips(=yes) + 0.0078 * IIEF_{preoperative} * FP.}$$

Hereafter, the predicted postoperative IIEF can be calculated as 30 * exp(y)/(1 + exp(y)).
The R2 for this model was 43% (adjusted R2 = 42%). Correlation between fitted and observed IIEF was 0.66. The accuracy of predictions is displayed in Figure 4F.

The interaction between preoperative IIEF and FP score is depicted in Figure 4A-C. The benefit of higher FP on the postoperative IIEF was shown to be larger with increasing baseline IIEF. The negative value of the coefficient for age illustrates the fact that with increasing age a decrease in the IIEFpostoperative was seen. The use of clips improved the postoperative IIEF outcome (Figure 4E). Due to the separation of the pedicles wherein the NVB is located, the use of clips is directly related to nerve-sparing without diathermia, which is accompanied by a ≈3 point increase in postoperative IIEF.
After variable selection, the dissection explained 38% variation of the IIEF (adjusted R2 = 37%), with a 5% decrease in the goodness of fit in R2 decreases when the FP information was omitted (Figure 4F).

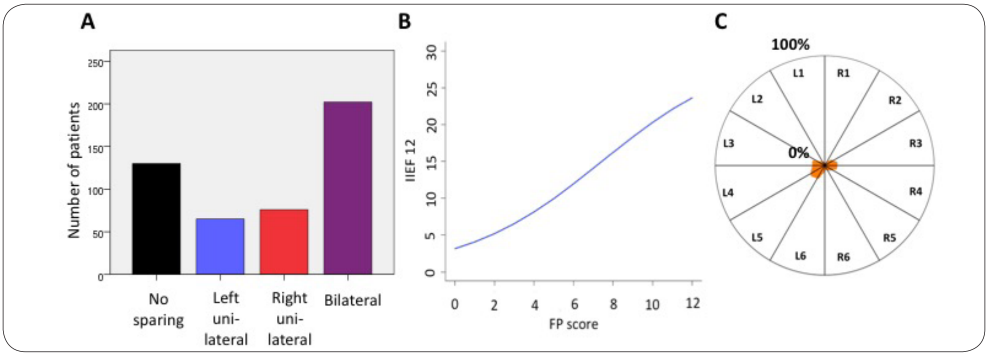

Figure 3. Average IIEF score at 12 months in relation to FP:

A) Frequency of nerve sparing based on laterality, **B)** The trend between the total FP score and IIEF at 12 months (blue line). **C)** The importance of individual FP segments (%) in relation to the postoperative IIEF as presented in (orange).

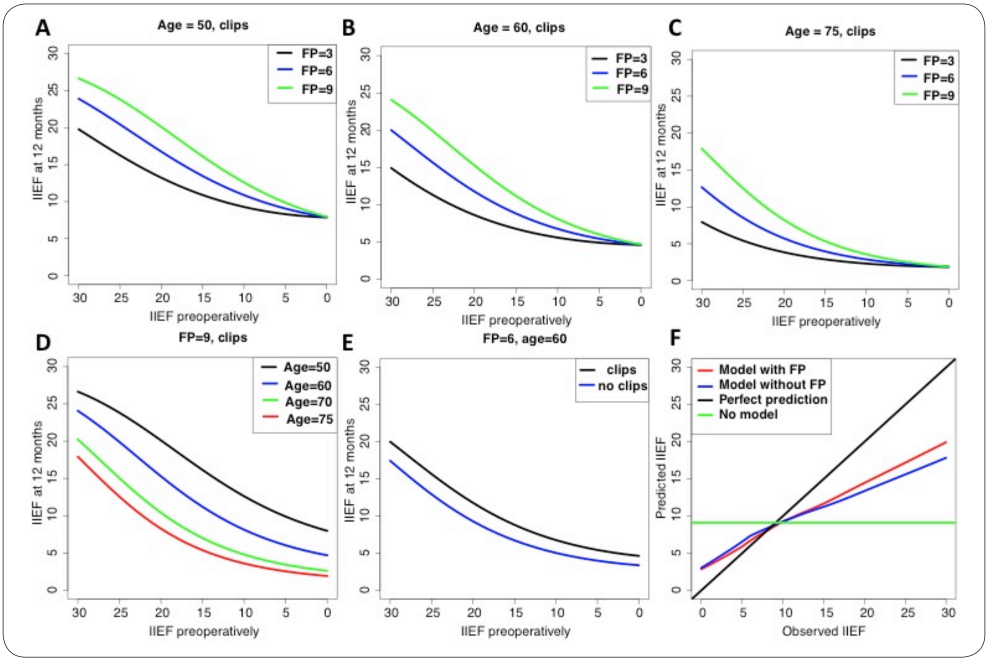

Figure 4. Outcome in the current cohort as predicted by our prediction model.

A-C) The influence of age (50, 60, and 70 years) in relation to FP score (FP = 3, 6, or 9). **D)** Comparison of the slopes of FP 9 curves for the age groups 50, 60, 70, and 75 years. **E)** Illustration of the influence of clip use. **F)** The relationship between actual and predicted IIEF based on the prediction score based on the prediction model was compared to use of no model for prediction (green line) and to the perfect prediction.

DISCUSSION

In the multivariable analysis, the FP score obtained during RARP was shown to be an important variable for the prediction of EF recovery together with patient's age, preoperative IIEF score, CCSI and use of clips for nerve sparing. The successful generation of a prediction model provides an important first step towards empowering the urologist to, in the future, realize a more personalized (precision) management of the EF in relation to radical surgery.

Literature indicates that bilateral nerve sparing, irrespective to the quantity of nerves spared, is more favorable compared to unilateral sparing [16,17]. In our cohort bilateral sparing also yielded superior outcomes, irrespective of the amount of fascia spared. Based on the FP score, we were able to further assess the contribution of the different preserved FP segments. Underlined by previous studies, our immunohistochemical findings (Figure SI1 and SI2) indicate that nerves related to EF were located mainly in the NVB dorsolateral to the prostate [18]. In line with these results, segment number R4 and L4 both displayed the strongest correlation with postoperative EF. A possible explanation for this effect might be found in the high nerve density per mm^2 in these FP regions and the fact that these FP segments were among those most frequently conjointly preserved (FP 4-6). Nevertheless, sparing of the more anteriorly located fascia and nerves (FP segments R1-R2 and L1–L2; see Figure SI1) did contribute to a further improvement of postoperative EF with an estimated benefit of 5-10% (Figure 4C). As supported in our immunohistochemical nerve analysis (SI1), these observations are in line with the presence of nerve structures in these areas. This finding also supports earlier reports that indicate that nerves are present in the entire circumference of the prostate [5–7,19–21].

It is generally assumed that EF recovery after surgery is age dependent, hereby accounting for the negative impact of older age on EF outcome. Similar to our observations Mandel et al. [22] found a strong negative correlation between age and EF outcome after surgery [23]. A higher FP score was associated with improved EF outcome at all ages and the slope of postoperative IIEF score as a function of preoperative IIEF score was similar for all ages. This supports the argument that nerve preservation in older men could also be attempted and that although they often have diminished preoperative EF, fascia preservation at older age may still result in a relative improvement of outcome similar to that for younger men.

Kang et al. described an EF prediction model based on the intraoperative technique used, laterality (bilateral vs. unilateral), nerve sparing grading (NS 1-10), and age [24]. We found that besides a patient' age, the FP score and use of clips instead of bipolar diathermia for prostate pedicle control were significant predictive factors in the nomogram. Kang et al. based their study on a EF cut-off value, a feature that is complicated given the variety cut-off values reported in literature [1,9,10,13,22,24,25]. We reasoned that a continuous score provides insight into the relative function loss and therefore better reflects the surgical impact in clinical practice where most men are able to assess their erectile function in a more continuous scale than as a dichotomous condition [24].

A limitation of the current study is its retrospective design. Ideally this nomogram, or a derivative, will in the future be used for virtual EF prediction and as such guide the surgical approach. To prove that indeed the nomogram can help to improve EF outcome, such a study will need to have a randomized setup. Prospectively, however, the nomogram can still be helpful during counseling. Moreover, in a postoperative setting there is less concern with the effects of data sampling: all data including the intraoperative FP score were prospectively obtained and documented in a standardized, ethically approved database. Hence, retrospective chart analysis with the associated limitations was not required. A second limitation of this study is the use of the IIEF score as outcome measure for EF, rather than an erection hardness test or other more physical assessments of EF [26]. Although earlier studies do support the use of questionnaires in EF assessment, it should be noted that originally the IIEF questionnaire was not designed for postoperative EF assessment.
When validated in other populations the prediction model will provide patients and care-givers a qualitative estimation of EF outcome after RARP. Future studies should be initiated to validate the nomogram, as such, prospectively generated feedback can be provided to improve its accuracy further e.g. by including imaging variables such as fascia thickness or nerve density as assessed on preoperative MRI [27]. Additionally, in the near future intraoperative fluorescence imaging of nerves may help improve the accuracy of nerve preservation [28,29].

CONCLUSION

In this study a quantitative nerve-sparing scoring technique during RARP was validated and integrated into a multivariate prediction model, which includes age, use of surgical clips, CCI, and preoperative EF. More anterior fascia preservation was correlated with better EF outcome and age was a strong independent predictor of EF outcome. In older men the relative benefit of more extensive fascia preservation was at least similar to younger men, despite a lower baseline IIEF score.

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SUPPLEMENTAL INFORMATION (SI)

METHODS

Patients

1241 men whom underwent robot assisted radical prostatectomy (RARP) at the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI-AvL) between September 2007 and November 2014 were included in this study (SI Table 2). Exclusion criteria included any prior local therapy (radiation, HIFU, cryoablation, TURP) or androgen ablation. Tumors were clinically and pathologically staged (TNM 2009, 7th edition) and graded according to Gleason sum score. Ethical approval for the execution of this study was provided by the institutional review board (IRB) of the NKI-AvL.

International index of erectile function – Erectile Function 5

All data recorded during treatment and follow-up was documented in the prospective database of the Department of urology of the NKI-AVL, which was approved by the IRB of the NKI-AVL. For evaluation of EF, patients were asked to fill out a self-administered erectile function evaluation tool (IIEF-EF5 later referred to as IIEF; Supplemental Information (SI), Table SI1) [1–4] prior to undergoing RARP (baseline IIEF) and at 12 months after the procedure (postoperative IIEF; recorded between nine and fifteen months).
As consensus on the optimal cut-off for ED based on IIEF score is lacking, a continuous read-out of the IIEF score (which provides better insight into the relative function loss (independent of IIEF scaling) during comparison of preoperative and postoperative IIEF) was used [1,2,4].

Comorbidity

Comorbidity was preoperatively scored using the CCIS [5] (Table SI1). For statistical analysis, the CCIS without age correction was divided into the following two groups, the group with score 0 and the group with CCIS >0 [5].

Surgical procedure

Fascia preservation was defined as the presence of a continuous fascia segment from base to apex without clinically visible interruptions after prostate removal. The extent of fascia sparing during RARP was then quantified as the FP score that ranged from 0-6 on both sides, with a total score between 0 and 12. Nerve preservation was attempted in patients who requested erectile function preservation, which had no evidence of extracapsular disease and a Gleason score of <7 ipsilaterally. Prostate pedicle vasculature dissection was performed either using careful bipolar coagulation or by using 10mm titanium clips (Aesculap, Inc., Center Valley, USA).

LND was performed in patients with a nomogram estimated risk of nodal metastases exceeding 5% and was generally executed after prostate removal [6].

Immunohistochemistry

Harvested tumor tissue was formalin-fixed and paraffin-embedded. Five µm sections were stained for general tissue characteristics (heamatoxylin and eosin; H&E) and the presence of nerves was evaluated through staining myelin.

Heamatoxylin and eosin staining

For the H&E staining, deparaffinized and rehydrated tissue sections were incubated for 10 min with heamatoxylin, rinsed in tap water for 10 min, incubated in eosin (5 min) and extensively rinsed with MilliQ, dehydrated and mounted (Estellan; Merck Millipore, Amsterdam, The Netherlands).

Myelin staining

For the myelin staining, tissue sections were deparaffinized and rehydrated after which an endogenous peroxidase inhibition step in 0.3% H2O/PBS was performed. After rinsing (PBS, PBS, PBS/0.05% Tween), sections were incubated overnight with a polyclonal-rabbit-anti-S100 antibody (1:4000; cat no. Z0311; Dako, Heverlee, Belgium). The next day, sections were rinsed (PBS, PBS, PBS/0.05% Tween), incubated with a secondary goat-anti-rabbit-biotin antibody (1:200; cat no. BA-1000; Vector Laboratories Inc., Burlingame, CA, USA) and normal goat serum (1:66; cat no. S-1000; Vector Laboratories Inc., Burlingame, CA, USA) for 1 h, rinsed again (PBS, PBS, PBS/0.05% Tween), and incubated for 1 h with ABC-reagents (Vector Laboratories Inc., Burlingame, CA, US) rinsed (PBS, PBS, PBS/Tris maleate), developed with 3,3’-diamobenzidine tetrahydrochloride (Sigma-Aldrich, Zwijndrecht, the Netherlands) and slightly counterstained with hematoxylin after which they were dehydrated and mounted (Estellan).

SI Tables

Table S1. Patient characteristics of responders with IIEF questionnaire results

Total (number)	1241
Number of patients that did not fill in the queries	252
Number of patients that filled in the preoperative queries	989
Number of patients that filled in the postoperative queries	566
Number of patients that filled in both the pre- and post operative queries (only these patients were used for further analysis)	473
BMI, median (IQR) (kg/m^2)	25.98 (24.24 – 27.78)
Age, median (IQR) (years)	63 (59 – 67)
PSA-level (ng/mL), median (IQR)	8 (5.8 – 12.0)
Preoperative International Index of Erectile Function (IIEF-EF) score, median (IQR)	21 (8 – 29)
Clinical T-stage	
- cT1 (%)	128 (27%)
- cT2 (%)	272 (58%)
- cT3 (%)	70 (15%)
Missing %	3 (0%)
Biopsy Gleason sum score	
- 4-6 (%)	242 (51%)
- 7 (%)	174 (37%)
- 8-10 (%)	57 (11%)
Clinical N-stage	
- cN0 (%)	201 (43%)
- cN1 (%)	9 (2%)
- cNx (%)	263 (56%)
Pathological T-stage	
- pT0 (%)	3 (1%)
- pT2 (%)	351 (74%)
- pT3 (%)	108 (23%)
- pT4 (%)	11 (2%)
Pathological Gleason sum score	
- 0 (0%)	1 (0%)
- 5-6 (%)	156 (33%)
- 7 (%)	255 (54%)
- 8-10 (%)	60 (12%)
Pathological N-stage	
- pN0 (%)	206 (44%)
- pN1 (%)	38 (8%)
- pNx (%)	229 (48%)
Tumor side	
Left (%)	31 (7%)
Left + Right (%)	401 (85%)
Right (%)	38 (8%)
Missing (%)	3 (1%)
Charlson comorbidity index score (CCIS)	
0 (%)	383 (81%)
+1 (%)	90 (19%)
Smoker	
Yes (%)	409 (88%)
No (%)	57 (12%)
Alcohol use	
None (%)	85 (18%)
<8 (%)	139 (30%)
8-14 (%)	122 (26%)
>14 (%)	121 (26%)
Intraoperative techniques	
FP (median, IQR)	4 (0 -6)
Clips yes	80 (17%)
Clips no	390 (83%)
Lymph node dissection	246 (52%)
No lymph node dissection	227 (48%)

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	Points IIEF score											
	0		1		2		3		4		5	
1. How often were you able to get an erection during sexual activity	No sexual activity		Almost never or never		A few times (much less than half the time)		Sometimes (about half the time)		Most times (much more than half the time)		Almost always or always	
Percentage preoperative and postoperative	16.1%	24.5%	5.0%	37.6%	11.4%	8.4%	6.7%	8.7%	11.6%	8.0%	49%	12.7%
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	No sexual activity		Almost never or never		A few times (much less than half the time)		Sometimes (about half the time)		Most times (much more than half the time)		Almost always or always	
Percentage preoperative and postoperative	17.7%	27.7%	10.1%	42.7%	7.8%	7.2%	7.2%	5.9%	8.9%	5.7%	48.4%	10.7%
3. When you attempted intercourse, how often were you able to penetrate (enter) your partner?	Did not attempt intercourse		Almost never or never		A few times (much less than half the time)		Sometimes (about half the time)		Most times (much more than half the time)		Almost always or always	
Percentage preoperative and postoperative	28.5%	38.5%	8.2%	34.3%	8.0%	5.7%	4.6%	5.7%	7.8%	5.1%	42.7%	10.8%
4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did not attempt intercourse		Almost never or never		A few times (much less than half the time)		Sometimes (about half the time)		Most times (much more than half the time)		Almost always or always	
Percentage preoperative and postoperative	31.9%	43.6%	5.7%	30.9%	7.6%	6.1%	5.1%	4.4%	10.5%	5.5%	39.1%	9.5%
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did not attempt intercourse		Extremely difficult		Very difficult		Difficult		Slightly difficult		Not difficult	
Percentage preoperative and postoperative	31.7%	54.1%	4.4%	17.7%	2.7%	4.9%	7.0%	5.3%	12.7%	7.4%	41.4%	10.5%
15. How do you rate your confidence that you could get and keep an erection?			Very low		Low		Moderate		High		Very high	
Percentage preoperative and postoperative	1.3%	0.8%	11.2%	48.8%	10.1%	17.5%	23.9%	16.5%	41.1%	12.1%	21.3%	4.2%

Table S2 IIEF score (preoperative and 12 months after prostatectomy)

Note: Questions in this questionnaire are not necessarily related to erectile dysfunction, but could also be related to the patients drive for sexual activity e.g. “Did not attempt intercourse” or “No sexual activity”.

RESULTS

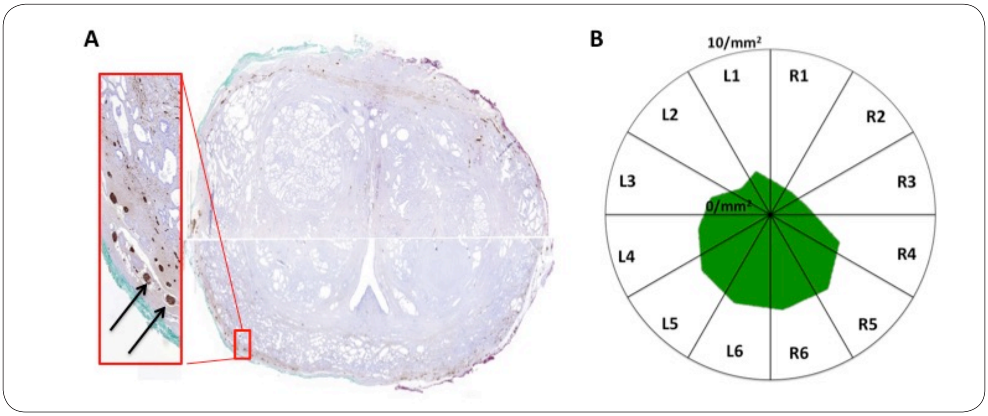
Pre- and postoperative IIEF outcome

The patient characteristics of the cohort with follow-up (n = 473) are presented in Table SI1. The median preoperative IIEF was 19 (Figure 2A), while the median postoperative IIEF (twelve months post surgery) was 6 (IQR 3-9; Figure 2A &B). Concurrently, the vast majority of the patients reported lower IIEF scores after prostatectomy (Figure 2C), indicating surgery-induced side effects. Unexplainably, in some cases increases in IIEF were also reported. We consider this as a reflection of the subjective nature of erectile dysfunction.

Comparison of unilateral and bilateral sparing

In some patients only the lower FP regions were spared (n = 140 unilateral and n = 99 bilateral). In the patients were the upper/higher FP regions R1 – R3 and L1 – L3 were spared (n = 70 for unilateral and n= 104 for bilateral sparing) this generally coincided with sparing of the lower regions (n= 343; 72.5%). Not all patients received bilateral sparing (Figure SI2D; n = 141), unilateral sparing was performed on both the left (n = 76; Figure SI2B) and right side (n= 65; Figure SI2C). Even when these groups were split the focus on the lower FP regions remained dominant, whereby sparing of the FP 4 and 5 regions was most prevalent.

To illustrate the effect of unilateral vs. bilateral nerve sparing regarding the mean drop in IIEF after prostatectomy, we compared the unilateral approach with the same FP and bilateral sparing for every FP score up to 6. For a total score of FP 2 with unilateral sparing there was a mean drop in IIEF after prostatectomy of 13 compared to 7.4 in IIEF with bilateral sparing (Mann Whitney U test, p-value = 0.051). In the patients with total FP of 3 the mean drop in IIEF for unilateral sparing was 14.3 and for bilateral 9.4 (Mann Whitney U, p-value 0.208). In the patients with total FP of 4, unilateral sparing resulted in a mean drop in IIEF of 11.8 after prostatectomy and for bilateral sparing a drop of 10.9 was seen (Mann Whitney U, p-value 0.579). In patients with a total FP score of 5 the mean drop in IIEF was lower for the unilateral group as compared to the bilateral group (9.9 vs. 10.9 respectively, p-value 0.794). In the total FP 6 group bilateral sparing resulted in a non-significant lower drop in IIEF when unilateral sparing was applied compared to bilateral sparing (6.5 vs. 9.7 respectively; p-value 0.320).



Pathological analysis of the nerve spread over the FP regions

Figure SI1. Pathological evaluation of the nerve distribution in different FP-regions of the prostate (n = 10).

A) Representative pathological image of the whole prostate (right) revealing nerves in the fascia (zoom-in of left showing stained nerves as indicated by the arrow).

B) Spider plot presenting the number of nerves per mm^2 per FP-region (average of ten patients that did not receive nerve-sparing). The individual values are provided in Figure SI2.

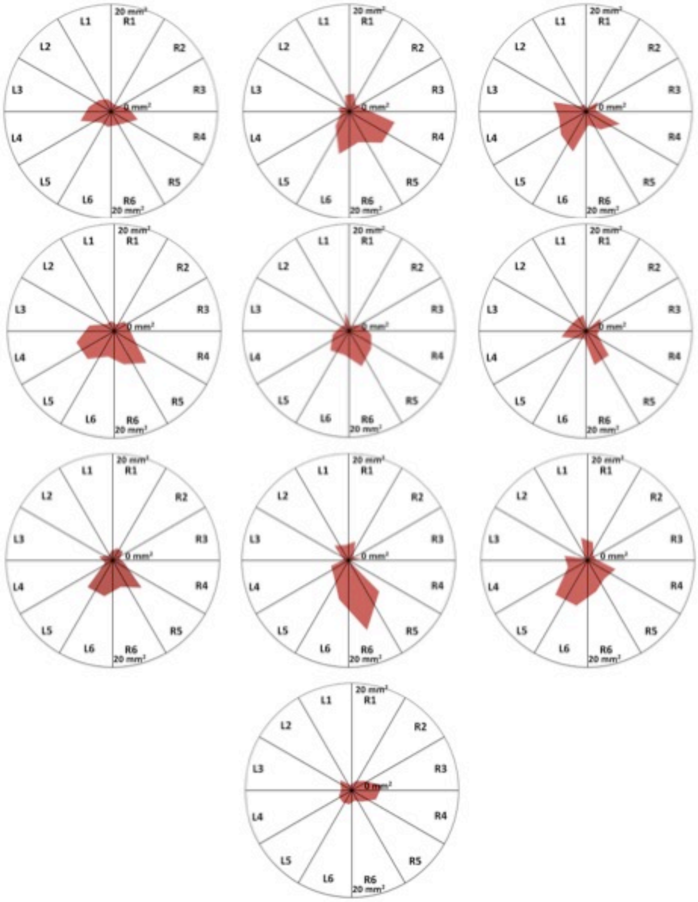


Figure SI2. Variation in nerve distributions per PF region in ten individual FP0 prostate samples.

Nerve distribution calculated in nerves per mm^2 per evaluated patient with a FP 0 score. In general the number of nerves was highest in the lower located quadrants.

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Immunohistochemical staining

Quantitative assessment of immunohistochemical staining of myelin containing nerves (Figure SI1A) revealed the average number of nerves in the individual FP regions and the overall distribution of these nerves. In line with literature [7, 8], the highest density of nerves was found in the lower FP regions L3-L6 and R3-R6 (Figure SI2B). It should, however, be noted that the variance observed between the individual patients was large, underlining the need for personalized resection methods (Figure SI3).

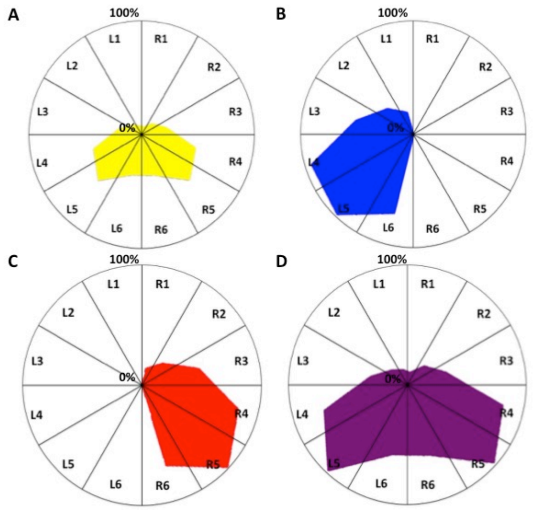

Figure S3. Surgical sparing of FP regions (n=473)

A) Overall percentile distribution of the FP regions spared during surgery of the total group (FP 0 patients included; n = 473; yellow).

B) Pattern of saving in patients that only received unilateral sparing on the left side (n= 65; blue),

C) on the right side (n =76; red), and **D)** after bilateral sparing (n = 202; purple).

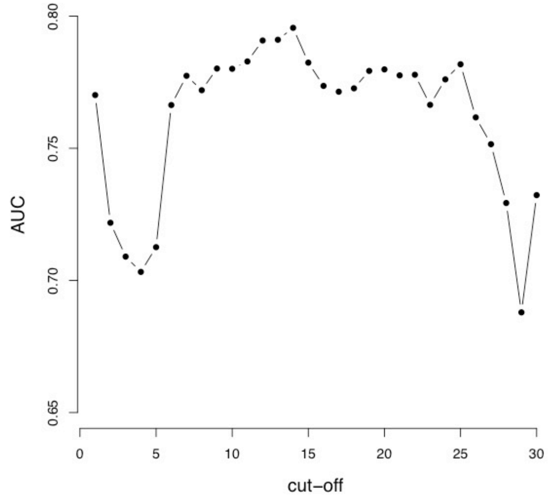

Figure S4. Relationship between the IIEF cut-off classifying patients into ED and no ED versus AUC for the model predicting ED with FP score.

In previous studies different cut-off values were used for IIEF score-based evaluation of ED. [3] However, placement of the cut-off value can directly influence the classification of patients into ED and no ED and the predictive value of the total FP score (Figure SI4). The highest area under the curve (AUC) was estimated when ED was defined as IIEF<14.

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