ORIGINAL ARTICLE

A prediction model relating the extent of intraoperative fascia preservation to erectile dysfunction after nerve-sparing robot-assisted radical prostatectomy

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Abstract

Robot-assisted radical prostatectomy (RARP) is performed in patients with prostate cancer. Unfortunately, 10–46% of patients may still suffer from limited erectile function (EF) after RARP. This study aimed to develop a prediction model based on the extent of fascia preservation (FP) and postoperative EF after RARP. A previously developed FP score quantizing the extent and regions of nerve-preservation was determined in a cohort of 1241 patients who underwent RARP. The predictive value of the FP score for post-prostatectomy EF (following the international index erectile function (IIEF) score, EF domain) was analyzed. To increase the predictive value of the scoring system, the FP regions were related to postoperative EF, nerve distribution and co-morbidity factors. Finally, a prediction model for EF was developed based on the studied cohort. When corrected for the preoperative IIEF-EF, the FP score was shown to be a significant denominator for IIEF ($p = 2.5 \times 10^{-15}$) with an R^2 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. Furthermore, patient's age, preoperative IIEF score, CCIS and use of clips for nerve sparing were significantly associated with postoperative IIEF-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-EF score. Quantitative nerve-sparing FP scoring could be related to the postoperative IIEF-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-EF. When further validated the prediction model could provide patients and care-givers a qualitative estimation of EF outcome after RARP.

Keywords Prediction model · Erectile dysfunction · RARP · Prostatectomy · Nerve-sparing · IIEF

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Introduction

Robot-assisted radical prostatectomy (RARP) is frequently performed in patients with clinically localized prostate cancer. While the use of robotics 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. Unfortunately, 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]. The FP-score accounts for the full circular distribution of the periprostatic nerves via a 12-tier score (Fig. 1a). As the resulting ± 1 cm 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
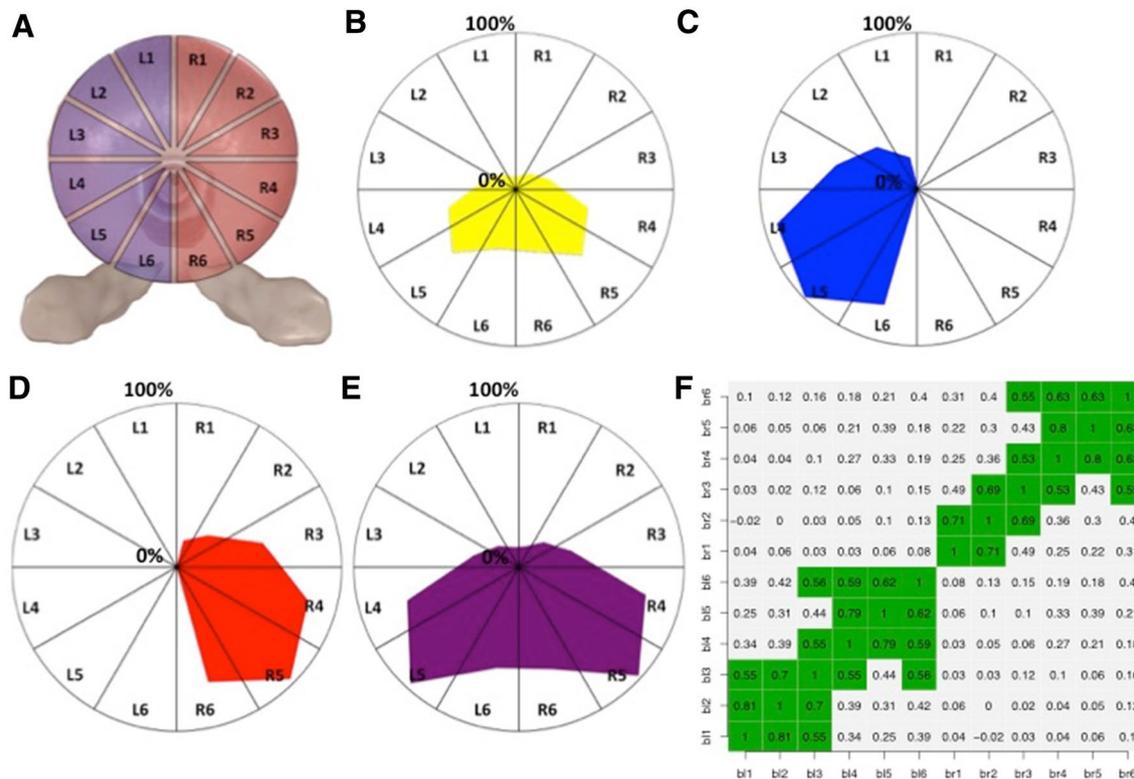

Fig. 1 Surgical sparing of FP regions ($n = 473$): **a** schematic overview of the different FP locations (left in blue and right in red). **b** Illustration of the overall percentile distribution of the FP segments spared during surgery of the total group (FP 0 patients included, $n = 1241$; yellow). 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

resections. With such a scoring system, 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. Such a prediction model could facilitate preoperative assessment of the potential value of the complex and time-consuming nerve preservation approaches. Furthermore, it could aid the urologist in providing personalized patient counseling, managing expectations, and as such, help optimize the balance that should be struck between radical tumor excision and EF preservation.

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 IIEF-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.

Patients and 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 at 12 months postoperatively (in a total of 473 patients that filled in the IIEF questionnaire). All 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 as previously described [13]. In a reproducibility analysis, three observers agreed on the score in 19 of 20 cases where in 1 one case a 1 point difference among observers was reported.

Statistical analysis

Patient, tumor and surgical characteristics of the study 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 R^2, 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 IIEFs were transformed back, realizing an interpretable value of the predicted IIEF. For exploratory 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: $IIEF_{preoperative} \times FP$ score, $IIEF_{preoperative} \times age$ and FP score $\times$ age. Variable selection was performed using the Akaike information criterion (AIC). Goodness of fit was evaluated using R^2 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 Fig. 1. The median FP score was 4 (interquartile range IQR 0–6), and 17% of patients who underwent a RARP presented a 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 (Fig. 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-EF score at 12 months after RARP (postoperative IIEF-EF; Fig. 2; Table SI2) and the total FP score was 0.5 (Fig. 3b). When corrected for the preoperative IIEF, the FP score was shown to be significant denominator for IIEF ($p = 2.5 \times 10^{-15}$; Fig. 3b) with an R^2 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 R^2 of 38%

(adjusted R^2 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-EF outcome (Fig. 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.
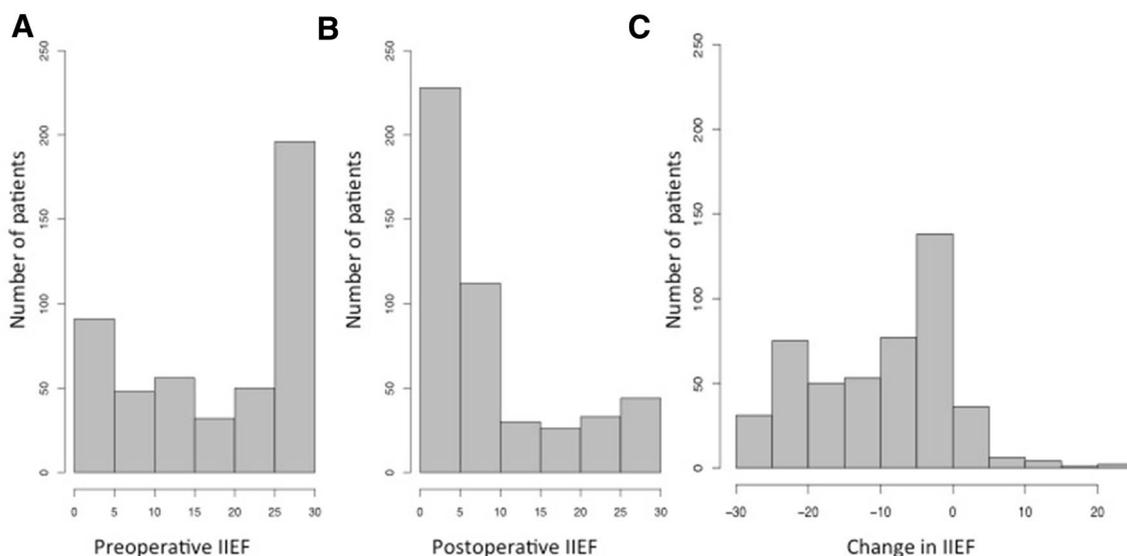

Fig. 2 Pre- and postoperative frequency histograms of IIEF and change in IIEF after 12 months ($n = 473$): **a** preoperative IIEF scores; **b** postoperative IIEF-EF at 12 months; **c** postoperative changes in IIEF-EF
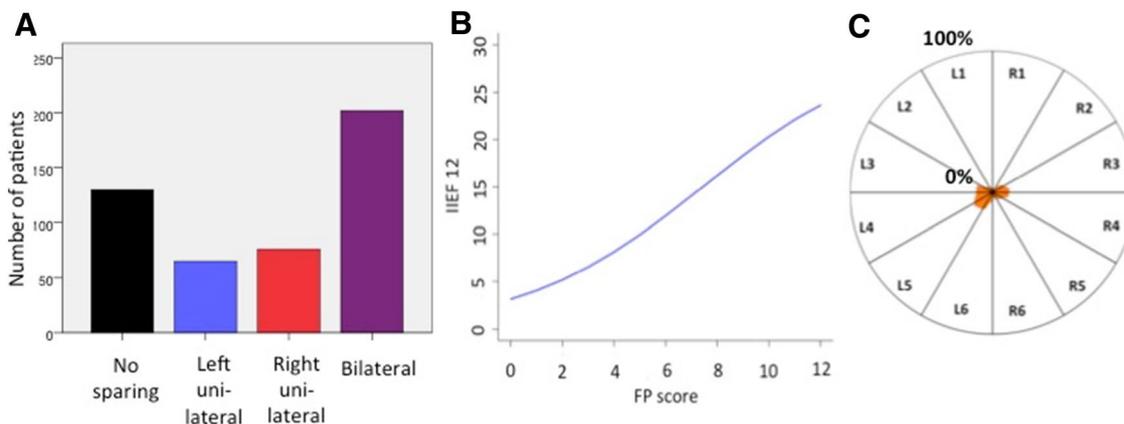

Fig. 3 Average IIEF-EF score at 12 months in relation to FP: **a** frequency of nerve sparing based on laterality, **b** the trend between the total FP score and IIEF at 12 months (blue line). **c** The importance of individual FP segments (%) in relation to the postoperative IIEF as presented in (orange)

Prediction model

Age, CCIS, smoking, alcohol intake, preoperative IIEF-EF score, FP score, use of clips and lymph node dissection were considered potentially predictive for the postoperative IIEF-EF (Table 1). Univariable linear regression showed that all covariates, apart from alcohol intake and smoking, were significantly associated with postoperative IIEF-EF. 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:

$$\hat{y} = \text{logit(IIEF)} = 1.95 - 0.0168 \times \text{IIEF}_{\text{preoperative}} + 0.0017$$
$$\times \text{IIEF}^2_{\text{preoperative}} - 0.0671 \times \text{age} + 0.0021 \times \text{FP}$$
$$+ 0.3651 \times \text{clips}(= \text{yes}) + 0.0078 \times \text{IIEF}_{\text{preoperative}} \times \text{FP}.$$

Hereafter, the predicted postoperative IIEF can be calculated as $30 \times \exp(\hat{y})/(1 + \exp(\hat{y}))$.

The R^2 for this model was 43% (adjusted $R^2 = 42\%$). Correlation between fitted and observed IIEF was 0.66. The accuracy of predictions is displayed in Fig. 4f.

The interaction between preoperative IIEF and FP score is depicted in Fig. 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 IIEF$_{\text{postoperative}}$ was seen. The use of clips improved the postoperative IIEF outcome (Fig. 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 $a \approx 3$ point increase in postoperative IIEF.

After variable selection, the dissection explained 38% variation of the IIEF (adjusted $R^2 = 37\%$), with a 5% decrease in the goodness of fit in R^2 decreases when the FP information was omitted (Fig. 4f).

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.

The literature indicates that bilateral nerve sparing, irrespective to the quantity of nerves spared, is more favorable compared to unilateral sparing [9, 16]. 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 [17]. 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

Table 1 List of predictors of transformed IIEF after prostatectomy

Predictors	Frequency or median (IQR)	Missing	Beta (on logit scale)	p value
Age	63 (59–67)	0 (0%)	− 0.1249	< 0.001
Preoperative IIEF	21 (8–29)	0 (0%)	Non-linear	< 0.001
Charlson Comorbidity Index Score (without age) 0 vs. 1+	–		− 0.4818	0.02626
Smoker	57 (13%)	7 (1%)	− 0.2819	0.28192
Alcohol use		6 (1%)		
< 8 units alcohol per week	139 (29%)	–	0.3076	0.16248
8–14 units alcohol per week	122 (26%)	–	0.308	0.24028
> 14 units alcohol per week	121 (26%)	–	0.3636	0.1670
Intraoperative variables				
FP score	4 (0–6)	0 (0%)	0.2876	< 0.001
Use of clips	80 (17%)	3 (1%)	1.0683	< 0.001
Lymph node dissection	246 (52%)	0 (0%)	0.6449	0.00014

Table shows the patient characteristics and intraoperative technique variables that were forced into the selection for the prediction model
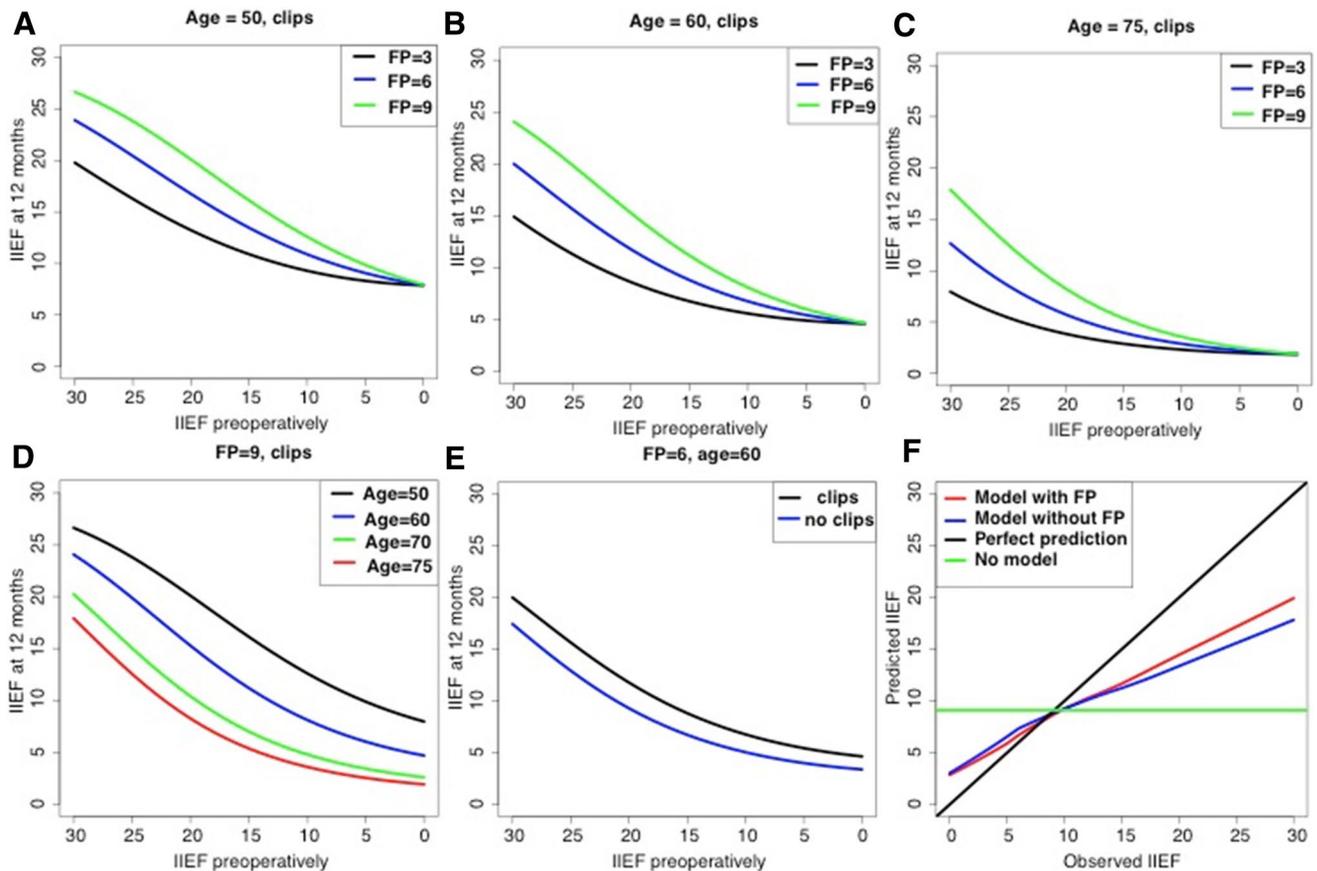
Fig. 4 Outcome in the current cohort as predicted by our prediction model. **a–c** The influence of age (50, 60, and 70 years) in relation to FP score (FP=3, 6, or 9). **d** Comparison of the slopes of FP 9 curves for the age groups 50, 60, 70, and 75 years. **e** Illustration of the influence of clip 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

with an estimated benefit of 5–10% (Fig. 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, 18–20].

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. [21] found a strong negative correlation between age and EF outcome after surgery [22]. 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 [23]. 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 of cut-off values reported in the literature [1, 9, 10, 13, 21, 23, 24]. 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 [23].

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 the nomogram can help to improve EF outcome, further study is needed. For the time being, 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-EF score as outcome measure for EF, rather than an erection hardness test or other more physical assessments of EF [25]. 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. Still we feel that predicting postoperative IIEF-EF score and compare it to preoperative IIEF-EF may provide patients with a more quantitative estimation of postoperative outcome, in particular since no cutoff definition for IIEF-EF domain score has been generally accepted.

When further validated the prediction model could 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 further improve its accuracy, e.g. by including imaging variables such as fascia thickness or nerve density as assessed on preoperative MRI [26]. Additionally, in the near future intraoperative fluorescence imaging of nerves may help improve the accuracy of nerve preservation [27, 28].

Conclusions

In this study, a quantitative nerve-sparing scoring technique during RARP was validated and integrated into a multivariate prediction model. 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, CCIS and use of clips for nerve sparing as compared to management of the prostate pedicle with bipolar coagulation. 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-EF score. When further validated the prediction model could provide patients and care-givers a qualitative estimation of EF outcome after RARP.

Compliance with ethical standards

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