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Exploratory Decision-Tree Modeling of Data from the Randomized REACTT Trial of Tadalafil Versus Placebo to Predict Recovery of Erectile Function After Bilateral Nerve-Sparing Radical Prostatectomy

Francesco Montorsi^{a,*,\$}, Matthias Oelke^{b,\$}, Carsten Henneges^{c,\$}, Gerald Brock^d, Andrea Salonia^a, Gianluca d'Anzeo^e, Andrea Rossi^e, John P. Mulhall^{f,\$}, and Hartwig Büttner^{g,\$}

^aDepartment of Urology, Vita Salute San Raffaele University, Milan, Italy

^bDepartment of Urology and Urological Oncology, Hanover Medical School, Hanover, Germany

^cGlobal Statistical Sciences, EU Statistics, Lilly Deutschland GmbH, Bad Homburg, Germany

^dDepartment of Surgery, Division of Urology, University of Western Ontario, London, Ontario, Canada

^eTherapeutic Area Men's Health, Eli Lilly SpA, Florence, Italy

^fMemorial Sloan Kettering Cancer Center, New York, NY, USA

^gBiomedicines BU, Lilly Deutschland GmbH, Bad Homburg, Germany

Abstract

*Corresponding author. Department of Urology, Vita Salute San Raffaele University, Via Olgettina, 60, 20132 Milan, Italy. Tel.: + 39 02 26437286; Fax: + 39 02 26437298. napoli.patrizia@hsr.it (for F. Montorsi).

^{\$}Contributed equally.

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Background—Understanding predictors for the recovery of erectile function (EF) after nerve-sparing radical prostatectomy (nsRP) might help clinicians and patients in preoperative counseling and expectation management of EF rehabilitation strategies.

Objective—To describe the effect of potential predictors on EF recovery after nsRP by post hoc decision-tree modeling of data from A Study of Tadalafil After Radical Prostatectomy (REACTT).

Design, setting, and participants—Randomized double-blind double-dummy placebo-controlled trial in 423 men aged <68 yr with adenocarcinoma of the prostate (Gleason 7, normal preoperative EF) who underwent nsRP at 50 centers from nine European countries and Canada.

Intervention—Postsurgery 1:1:1 randomization to 9-mo double-blind treatment with tadalafil 5 mg once a day (OaD), tadalafil 20 mg on demand, or placebo, followed by a 6-wk drug-free-washout, and a 3-mo open-label tadalafil OaD treatment.

Outcome measurements and statistical analysis—Three decision-tree models, using the International Index of Erectile Function-Erectile Function (IIEF-EF) domain score at the end of double-blind treatment, washout, and open-label treatment as response variable. Each model evaluated the association between potential predictors: presurgery IIEF domain and IIEF single-item scores, surgical approach, nerve-sparing score (NSS), and postsurgery randomized treatment group.

Results and limitations—The first decision-tree model ($n = 422$, intention-to-treat population) identified high presurgery sexual desire (IIEF item 12: 3.5 and <3.5) as the key predictor for IIEF-EF at the end of double-blind treatment (mean IIEF-EF: 14.9 and 11.1), followed by high confidence to get and maintain an erection (IIEF item 15: 3.5 and <3.5; IIEF-EF: 15.4 and 7.1). For patients meeting these criteria, additional non-IIEF-related predictors included robot-assisted laparoscopic surgery (yes or no; IIEF-EF: 19.3 and 12.6), quality of nerve sparing (NSS: <2.5 and 2.5; IIEF-EF: 14.3 and 10.5), and treatment with tadalafil OaD (yes and no; IIEF-EF: 17.6 and 14.3). Additional analyses after washout and open-label treatment identified high presurgery intercourse satisfaction as the key predictor.

Conclusions—Exploratory decision-tree analyses identified high presurgery sexual desire, confidence, and intercourse satisfaction as key predictors for EF recovery. Patients meeting these criteria might benefit the most from conserving surgery and early postsurgery EF rehabilitation. Strategies for improving EF after surgery should be discussed preoperatively with all patients; this information may support expectation management for functional recovery on an individual patient level.

Patient summary—Understanding how patient characteristics and different treatment options affect the recovery of erectile function (EF) after radical surgery for prostate cancer might help physicians select the optimal treatment for their patients. This analysis of data from a clinical trial suggested that high presurgery sexual desire, sexual confidence, and intercourse satisfaction are key factors predicting EF recovery. Patients meeting these criteria might benefit the most from conserving surgery (robot-assisted surgery, perfect nerve sparing) and postsurgery medical rehabilitation of EF.

Trial registration—[ClinicalTrials.gov](https://clinicaltrials.gov), NCT01026818

Keywords

Clinical trials; Decision-tree analysis; Erectile dysfunction; Nerve-sparing radical prostatectomy; Phosphodiesterase type 5 inhibitors; Predictors; Prostate cancer; Rehabilitation; Tadalafil

1. Introduction

The recovery of erectile function (EF) after bilateral nerve-sparing radical prostatectomy (nsRP) for prostate cancer (PCa) varies from patient to patient, depending on factors such as age, presurgery EF, comorbid conditions, and postsurgery follow-up time [1,2]. The impact of surgical approach [3], extent of nerve sparing during surgery [4,5], and postsurgery treatment with phosphodiesterase type 5 inhibitors (PDE5-Is) [6–9] on EF recovery has been studied extensively over the past few years.

Decision-tree modeling of study data [10] can be used to describe and visualize the effect of such potential predictors on postsurgery EF. This may help clinicians to identify which patient subgroups might benefit the most from conserving surgical techniques such as robot-assisted laparoscopy [2,3] and from daily PDE5-I treatment after nsRP [11].

Exploratory decision-tree modeling on the data of the randomized placebo-controlled trial, A Study of Tadalafil After Radical Prostatectomy (REACTT) [6], was applied to describe the effect of potential predictors on postsurgery EF, as measured by the International Index of Erectile Function-Erectile Function (IIEF-EF) domain score [12]. The REACTT trial was designed to investigate the effect of 9-mo double-blind treatment with tadalafil once a day (OaD) or on demand (PRN) on EF recovery. The randomized treatment period was succeeded by 6 wk of drug-free washout and 3 mo of open-label treatment with tadalafil OaD for all patients. The primary outcome was the proportion of patients achieving unassisted EF recovery, defined as an IIEF-EF domain score ≥ 22 following drug-free washout [6]. Both PDE5-I-assisted EF (at the end of double-blind treatment) and unassisted EF (after drug-free washout) were assessed. Tadalafil treatment (OaD or PRN), when compared with placebo, had no beneficial impact on unassisted EF at the end of washout, but postsurgery treatment with tadalafil OaD improved drug-assisted EF at the end of double-blind treatment versus placebo [6].

The objective of this post hoc decision-tree modeling was to describe the impact of presurgery IIEF-related patient characteristics, surgical approach, extent of nerve sparing during surgery, and postsurgery treatment with tadalafil OaD, PRN, or placebo on IIEF-EF domain scores at the end of the double-blind, washout, and open-label treatment periods of the study.

2. Patients and methods

2.1. Patients

All patients enrolled in REACTT were adult men, aged <68 yr at the time of nsRP, with normal presurgery EF (IIEF-EF ≥ 22 at screening) [6,13] who underwent nsRP for organ-confined nonmetastatic PCa (Gleason score ≤ 7 , prostate-specific antigen [PSA] <10 ng/ml).

Patients were enrolled between November 2009 and August 2011 at 50 centers in nine European countries and Canada; all had signed written informed consent [6].

2.2. Trial design

The multicenter phase 4 randomized double-blind, double-dummy three-arm placebo-controlled parallel-group trial was conducted in accordance with the Declaration of Helsinki; responsible ethical review boards approved the study protocol for each country. Detailed trial design and eligibility criteria are available at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01026818) (NCT01026818) and from Montorsi et al [6]. The trial consisted of a presurgery screening visit (after cancer diagnosis, 6 wk before nsRP), a postsurgery screening visit, 9-mo double-blind treatment with tadalafil 5 mg OaD, tadalafil 20 mg PRN, or placebo (1:1:1 randomization; treatment started within 6 wk after nsRP), 6 wk of drug-free washout, and 3 mo of open-label treatment with tadalafil 5 mg OaD (all patients) (Supplementary Fig. 1) [6]. During double-blind treatment, matching placebo tablets identical to the 5 mg and 20 mg tadalafil tablets were used to ensure that the blinded regimen was identical for all treatment groups. For PRN dosing, patients were permitted to take up to three tablets per week (and no more than one per day) [6].

2.3. Surgery

Investigators were asked to classify the surgical approach used into one of these four categories: robot-assisted laparoscopy, conventional laparoscopy, open surgery, and other surgery. One single site that conducted only endoscopic extraperitoneal radical prostatectomies reported this approach as “other” surgery. Clinically, these patients can be considered as undergoing conventional laparoscopy. The extent of intraoperative nerve sparing was assessed using the grading system described by Moskovic et al [14]. Surgeons assigned a nerve-sparing score (NSS) between 1 and 4 for each neurovascular bundle (left and right; 1 = complete preservation, 4 = complete resection). A total NSS of 2 was considered perfect, and any total NSS >2 was considered not perfect [6].

2.4. Main outcome measures

The primary outcome measure of REACTT was EF recovery (at the end of washout), defined as an IIEF-EF domain score ≥ 22 [6,12]. This cut-off was previously identified as a reliable score for defining EF recovery after nsRP [15]. For the decision-tree modeling of IIEF-EF response described here, the IIEF-EF domain score was used as a continuous response variable.

2.5. Statistical analysis

2.5.1. Sample size and analysis population—The planned sample size of 412 patients was discussed previously [6]. All analyses were based on the intention-to-treat (ITT) population that included all randomized patients with baseline data and at least one postbaseline visit. For the decision-tree modeling, patients with missing IIEF-EF data at a specific time point were excluded from the respective analysis; no imputation was performed.

2.5.2. Decision-tree modeling—Decision-tree modeling of data from the ITT population was performed to describe and visualize the effect of potential predictors on postsurgery IIEF-EF domain scores. Decision-tree modeling is an exploratory statistical method that can model a response variable, in this case the postsurgery IIEF-EF domain score, as it relates to patient characteristics from a sequence of hierarchical tests (yes/no decisions). The analysis software automatically generates the tests and then selects the optimal sequence of hierarchical decisions based on the information taken from the individual characteristics and its relevance to the response variable.

The resulting decision-tree model can be visualized as a graphical representation of the hierarchical decision sequence that splits the overall population into subgroups to describe the response variable [10,16]. All decision trees start with a root node at the top of the tree and split the data set into a hierarchy of subsets, denoted by branch-like segments, ending in leaves that are labeled with the mean response of the described subgroup. These graphs, following the decisions from the root to specific leaves, define patterns through the sequence of test decisions that describe the patients summarized by the leaf. The first decision next to the root has the highest predictive effect.

Three different decision-tree models were generated for the IIEF-EF domain score (response variable) at the end of double-blind, washout, and open-label treatment periods, respectively. This is consistent with previously disclosed results from this study because these time points were of primary interest in the study protocol as the time points for EF evaluation. The three time points represent EF recovery for three different treatment modalities: the assisted EF directly at the end of double-blind treatment, the unassisted EF after 1.5 mo of washout, and the evaluation of a carryover effect of the randomized treatment after rechallenge with the same treatment (tadalafil 5 mg OaD for all patients). The following patient characteristics were considered clinically important by the authors and were therefore included in the modeling: presurgery IIEF domain scores (EF, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) and all 15 presurgery IIEF single-item scores assessed at the initial screening visit, type of nsRP (robot-assisted laparoscopy, conventional laparoscopy, open surgery, other surgery), NSS as assessed during surgery, postsurgery treatment group (tadalafil OaD, tadalafil PRN, placebo), and age. Decision trees were generated using the Gini index as split criterion. The decision trees were pruned using leave-one-out cross-validation. Surrogate splits were used to handle missing data. No further adjustments were performed. Descriptive patient characteristics data were analyzed using SAS v.9.2 software (SAS Institute Inc., Cary, NC, USA). Decision-tree analysis was programmed using R v.2.15.1 (R Foundation for Statistical Computing, Vienna, Austria) [17], using the packages rpart v.2.01 [18] and rpart.plot v.1.4-3 [19].

3. Results

3.1. Patient disposition and baseline characteristics

Of 583 patients screened, 422 started randomized postsurgery treatment with tadalafil OaD (139 [32.9%]), tadalafil PRN (142 [33.6%]), or placebo (141 [33.4%]) (Supplementary Fig. 2; ITT population). Patient disposition, baseline demographics, and relevant disease characteristics were balanced in the three treatment groups (Table 1). As per inclusion

criteria, all patients had IIEF-EF domain scores ≥ 22 at the screening visit before nsRP. A total of 332 (78.7%), 320 (75.8%), and 307 (72.7%) patients with no missing data were included in the three decision-tree analyses of EF recovery at the end of the double-blind, washout, and open-label treatment periods, respectively.

3.2. Predicting erectile function recovery at the end of double-blind treatment

The first decision tree describing potential predictors for IIEF-EF at the end of double-blind treatment (Fig. 1; complete data in Supplementary Table 1) divided the patient sample into two branches with high and low sexual desire (IIEF item 12: ≥ 3.5 , $n = 210$; < 3.5 , $n = 122$) before they underwent surgery, associated with mean IIEF-EF scores at the end of double-blind treatment of 14.9 and 11.1 points, respectively. Most patients in the high sexual desire branch also had high confidence to get and maintain an erection before they underwent surgery (IIEF item 15: ≥ 3.5 , $n = 198$), and then achieved a mean IIEF-EF domain score of 15.4 points at the end of double-blind treatment. For this patient branch, the main predictor for a high IIEF-EF was postsurgery treatment with tadalafil OaD ($n = 67$), associated with a mean IIEF-EF domain score at the end of double-blind treatment of 17.6 points. The highest mean IIEF-EF domain score at the end of double-blind treatment (mean IIEF-EF: 25.9) was achieved in a small branch of seven patients who had received tadalafil OaD, had previously highly enjoyed sexual intercourse (IIEF item 8 ≥ 4.5), and with IIEF overall satisfaction domain scores < 9.5 (maximum score: 10) before they underwent surgery. Patient age was not included in this model.

For those patients who received tadalafil PRN or placebo ($n = 131$; mean IIEF-EF: 14.3 points), most reported high EF and at least a few intercourse attempts before surgery (IIEF-EF ≥ 28.5 , IIEF item 6 ≥ 1.5). Within this branch, a close-to-perfect NSS (< 2.5 , $n = 71$) and robot-assisted laparoscopy ($n = 18$) were the key EF predictors, associated with mean IIEF-EF scores at the end of double-blind treatment of 14.3 and 19.3 points, respectively.

3.3. Predicting erectile function recovery at the end of washout

The second decision-tree model describes potential predictors for IIEF-EF at the end of drug-free washout, that is, after the loss of PDE5-I effect [6] (Fig. 2; complete data in Supplementary Table 2). This model divided the patient sample into two branches with high and low intercourse satisfaction (IIEF domain score ≥ 12.5 , $n = 128$; < 12.5 , $n = 192$) before surgery, associated with mean IIEF-EF scores at the end of double-blind treatment of 15.6 and 11.4 points, respectively. For patients in the high intercourse satisfaction branch, the main predictor for high IIEF-EF was robot-assisted laparoscopy, associated with a mean IIEF-EF domain score of 19.6 points (mild erectile dysfunction) at the end of washout. The highest mean IIEF-EF domain score at the end of washout was achieved in a small branch of 12 patients who received robot-assisted laparoscopy and reported few intercourse attempts before surgery (IIEF item 6; < 3.5 ; mean IIEF-EF: 26.7 points). In this model, postsurgery PDE5-I treatment (tadalafil OaD, tadalafil PRN, or placebo) had no relevant impact on IIEF-EF at the end of washout; younger age (< 61 yr) was slightly predictive for higher IIEF-EF values. The branches including patients with lower intercourse satisfaction (IIEF domain score < 12.5), lower sexual desire (IIEF item 12 < 3.5), and lower confidence to get and

maintain an erection (IIEF item 15 <3.5) had low mean IIEF-EF domain scores <10 points at the end of washout.

3.4. Predicting erectile function recovery at the end of open-label treatment

The third decision-tree model described potential predictors for IIEF-EF at the end of the 3-mo open-label treatment with tadalafil OaD for all patients (Fig. 3; complete data in Supplementary Table 3). Again, the model divided patients into two branches with high and low presurgery intercourse satisfaction (IIEF domain score ≥ 11.5 , $n = 179$; <11.5, $n = 128$), associated with mean IIEF-EF scores of 18.9 and 14.1 points, respectively, at the end of open-label treatment. In the branch of patients with high intercourse satisfaction, the main predictor for a high IIEF-EF was robot-assisted laparoscopy, associated with a high mean IIEF-EF domain score of 22.3 points at the end of open-label treatment. Patient age and postsurgery PDE5-I treatment (tadalafil OaD, tadalafil PRN, or placebo) had only a minor predictive effect. The highest scores, corresponding to full recovery at the end of open-label treatment, were achieved in a branch of 33 patients who had received robot-assisted laparoscopy and had at least a close-to-perfect NSS ≤ 2.5 (mean IIEF-EF: 24.8 points) and in a small branch of nine patients who were aged <61 yr and had received tadalafil OaD or PRN and either robotic or laparoscopic surgery (mean IIEF-EF: 25.4 points).

4. Discussion

Understanding the impact of patient characteristics, type of surgical approach, and postsurgery treatment on EF recovery after nsRP can help clinicians manage patients' expectations in the preoperative planning phase, and engage patients and their partners in an early postoperative EF rehabilitation or preservation program. This exploratory decision-tree modeling of data from the REACTT trial identified presurgery sexual desire, sexual confidence, and intercourse satisfaction as key predictors for EF recovery after nsRP. Patients meeting these criteria seemed to benefit most (in terms of EF recovery) from postsurgery treatment with tadalafil OaD started early post-nsRP, or—if treated with placebo or tadalafil PRN—from robot-assisted laparoscopy with perfect nerve sparing.

These data are largely consistent with a systematic review by Briganti et al who identified “accurate patient selection” (based on age, preoperative EF, and comorbidity profile), adequate surgical technique (ie, preservation of neurovascular bundles), and pharmacologic treatment as the major determinants of postoperative EF [20]. In contrast, a 2014 analysis of potential predictors for EF recovery after 1 or 2 yr concluded that no variable other than the IIEF item 6 score (number of intercourse attempts) was significantly associated with patient outcome; age, cancer stage, grade, PSA level, nerve-sparing status, and baseline EF had no major impact [21].

Differing from a previous study, though [1], age did not seem to be a major predictor of better EF recovery in this analysis. In contrast, the association between robot-assisted laparoscopy and better EF recovery in patients with higher sexual desire and intercourse satisfaction before surgery was consistently seen in three different decision-tree models, that is, for EF recovery at the end of the double-blind, washout, and open-label treatment periods. The effect on EF recovery was most pronounced at the later time points (after

washout and after open-label treatment). These findings are also in line with previous REACTT trial analyses on the impact of surgical approach [3], with a meta-analysis by Kilminster et al [2] and several trials and case reports [22–27].

Nevertheless, it needs to be considered that this trial was not designed to evaluate the different types of surgery; the study did not account for the physicians' surgical volume or learning curve with respect to the specific surgical approach used [3]. Although robot-assisted surgery in particular seems to be associated with a long learning curve [28], we cannot exclude that the findings result from differences in surgical experience with a specific technique rather than from the different types of surgery used.

This trial was primarily designed to evaluate the effect of postsurgery treatment with tadalafil OaD or PRN versus placebo on EF recovery. In the primary analysis, treatment with tadalafil OaD or PRN had no beneficial impact on unassisted EF at the end of the drug-free washout (primary end point not met), but treatment with tadalafil OaD improved drug-assisted EF at the end of double-blind treatment versus placebo [6]. These findings are reflected in the post hoc decision-tree models reported here. In patients with high presurgery sexual desire and confidence, treatment with tadalafil OaD was associated with higher IIEF-EF values than tadalafil PRN or placebo at the end of the 9-mo double-blind treatment period, but not after 6 wk of drug-free washout or after 3 mo of open-label treatment with tadalafil OaD. The 9-mo treatment period was probably too short to achieve optimal EF recovery, and the patient population was relatively young, sexually active, and excluded men with certain comorbid medical conditions (eg, diabetes mellitus) [6].

A recent retrospective regression analysis study in a cohort of 196 patients also found that oral PDE5-I treatment (100 mg sildenafil, 20 mg tadalafil, or 20 mg vardenafil) and surgical approach (uni- or bilateral) were associated with improved EF recovery [28]. There was no difference if the oral PDE5-Is were given on demand or two or three times a week; one can only speculate if the impact would have been more pronounced with daily treatment.

The decision-tree models in the current study were optimized by data pruning to eliminate branches that were not predictive. Because the decision-tree modeling algorithm always takes the optimal decision for splitting at each node and keeps this decision, more predictive decision-tree models could have been missed. Although the decision trees are fairly robust in structure because the leave-one-out cross-validation technique was used, readers should be aware that the decision trees, like any other statistical model, may change in structure if variables are added or removed. Therefore, the decision trees should be viewed as descriptive analysis explaining the data, but they are not confirming predictors.

Also, the decision-tree analysis was performed post hoc, and the study was not specifically designed to identify predictors for EF recovery. The patient characteristics selected were based on the available data and the authors' clinical experience. Also, the results were obtained in a selected, relatively young patient population (age <68 yr; Gleason score 7). This might help to explain why the predictive effect of patient age was so poor in this analysis. Also, presurgery EF assessment was performed at screening (ie, after cancer diagnosis and biopsy). Although patients had to report no history of erectile dysfunction as

the entry criterion [6], the reliability of a baseline EF assessment using the IIEF-EF questionnaire in patients after PCa diagnosis is questionable because it may be affected by psychological stress and anxiety [29].

Finally, we cannot exclude that the categorical assessment of NSS might have been biased because it is a subjective measure self-rated by surgeons. Also, patients with a total NSS >4 (left plus right bundle), corresponding to poor nerve sparing, were excluded from the trial. Therefore, most patients enrolled in this trial had a perfect NSS of 2.

Despite these limitations, the current decision-tree analysis provides new insights on the potential impact of preoperative assessment of IIEF domains, surgical approach, and postsurgery PDE5-I treatment on EF recovery after nsRP.

5. Conclusions

Exploratory decision-tree modeling identified high presurgery sexual desire, confidence to get and maintain an erection, and presurgery intercourse satisfaction as key predictors for EF recovery (IIEF-EF) after nsRP. Patients meeting these criteria might benefit the most from conserving surgical techniques (robot-assisted laparoscopy, perfect nerve sparing), early postsurgery engagement in a rehabilitation program for EF, and treatment with tadalafil OaD. Strategies for improving EF after surgery should be discussed preoperatively with all patients; this information may support expectation management for functional recovery on an individual patient level.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Exploratory decision-tree modeling suggested that high presurgery sexual desire, sexual confidence, and intercourse satisfaction are key predictors for erectile function (EF) recovery after nerve-sparing radical prostatectomy. Patients meeting these criteria might benefit most from conserving surgery (robot assisted, perfect nerve sparing) and postsurgery medical rehabilitation and preservation of erectile function. Strategies for improving EF after surgery should be discussed preoperatively with all patients; this information may support expectation management for functional recovery on an individual patient level.

Fig. 1.

Decision-tree modeling ($n = 332$) to identify predictors for the International Index of Erectile Function-Erectile Function (IIEF-EF) domain score after 9 mo of double-blind treatment with tadalafil once a day (OaD), tadalafil on demand (PRN), or placebo. These patient characteristics were included in the model: mean IIEF single-item scores and mean IIEF domain scores at baseline (visit 1, before bilateral nerve-sparing radical prostatectomy [nsRP]; shown in red), variables related to surgery (shown in green), including the type of nsRP (robot-assisted laparoscopy, conventional laparoscopy, open surgery, or other), nerve-sparing score (collected at nsRP), and other factors related to the study design (in blue) such as randomized treatment (tadalafil OaD, tadalafil PRN, or placebo; started approximately 6 wk after nsRP) and patient age. The analysis software automatically generated the optimal hierarchy of the decision tree. Patient age had no predictive effect and is therefore not included in the tree. Text boxes ("nodes") show the decision-tree splits identified as best predictors for IIEF-EF domain scores at the end of double-blind treatment: IIEF data at baseline, nsRP and NSS data collected at visit 2, randomized treatment started at visit 4. Gray circles show the mean IIEF-EF domain scores at the end of double-blind treatment for the respective decision branch. At each node, patients who fulfill the criterion are always branched to the right, and patients who do not fulfill the criterion are branched to the left.

The thickness of each branch reflects the number of patients per branch (precise patient numbers are provided in Supplementary Table 1). Note: IIEF item 12 and the IIEF-Sexual Desire domain score (summarized from items 11 and 12) both reflect sexual desire, the IIEF-Intercourse Satisfaction domain score reflects satisfaction with sexual intercourse, IIEF item 15 reflects the confidence to get and maintain an erection, the IIEF-EF domain score reflects erectile function, IIEF item 6 reflects the number of sexual intercourse attempts, IIEF item 8 reflects the enjoyment of sexual intercourse, and the IIEF-Overall Satisfaction domain score reflects overall sexual satisfaction. IIEF = International Index of Erectile Function; IIEF-EF = International Index of Erectile Function-Erectile Function domain score; IIEF-IS = IIEF-Intercourse Satisfaction domain score; IIEF-SD = IIEF-Sexual Desire domain score; IIEF-OS = IIEF-Overall Satisfaction domain score; nsRP = bilateral nerve-sparing radical prostatectomy; NSS = nerve-sparing score; OaD = once a day; PRN = on demand; rTx = randomized treatment.

Fig. 2.

Decision-tree modeling ($n = 320$) to identify predictors for the mean International Index of Erectile Function-Erectile Function (IIEF-EF) domain score at the end of drug-free washout (month 10.5). These patient characteristics were included in the model: mean IIEF single-item scores and mean IIEF domain scores at baseline (visit 1, before bilateral nerve-sparing radical prostatectomy [nsRP], in red), surgery-related variables (in green), including the type of nsRP (robot-assisted laparoscopy, conventional laparoscopy, open surgery, or other), nerve-sparing score (collected at nsRP), and other variables related to study design (randomized treatment, patient age; in blue). Randomized treatment had no predictive effect and is therefore not included in this tree. White text boxes show the decision-tree characteristics the model identified as best predictors for IIEF-EF domain scores at the end of washout. Gray circles show the mean IIEF-EF domain scores at the end of washout for the respective decision branch. Note: IIEF item 12 reflects sexual desire, IIEF item 15 reflects the confidence to get and maintain an erection, IIEF item 6 reflects the number of sexual intercourse attempts; IIEF item 2 reflects the hardness of erection, IIEF item 14 reflects satisfaction with the sexual relationship with the partner, IIEF item 7 and the IIEF-Intercourse Satisfaction domain score both reflect satisfaction with sexual intercourse, and IIEF item 5 reflects the ability to maintain an erection until completion of intercourse.

IIEF = International Index of Erectile Function; IIEF-IS = IIEF-Intercourse Satisfaction domain score; nsRP = bilateral nerve-sparing radical prostatectomy; NSS = nerve-sparing score.

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Fig. 3.

Decision-tree modeling ($n = 307$) to identify predictors for the mean International Index of Erectile Function-Erectile Function (IIEF-EF) domain score at the end of open-label treatment with tadalafil once a day (OaD) for all patients (month 13.5). These patient characteristics were included in the model: mean IIEF single-item scores and mean IIEF domain scores at baseline (visit 1, before bilateral nerve-sparing radical prostatectomy [nsRP], in red), surgery-related variables including type of nsRP (robot-assisted laparoscopy, conventional laparoscopy, open surgery, or other) or nerve-sparing score, and other variables related to study design (in blue) including patient age and randomized treatment (tadalafil OaD, tadalafil on demand, or placebo). White squares show the decision-tree characteristics the model identified as best predictors for IIEF-EF domain scores at the end of open-label treatment. Gray circles show the mean IIEF-EF domain scores at the end of open-label treatment for the respective decision branch. Note: The IIEF-Intercourse Satisfaction domain score and IIEF item 7 both reflect satisfaction with sexual intercourse, the IIEF-Sexual Desire domain score reflects sexual desire, IIEF item 15 reflects the confidence to get and maintain an erection, IIEF item 8 reflects the enjoyment of sexual intercourse, the IIEF-Overall Satisfaction domain score reflects overall sexual satisfaction, IIEF item 6 reflects the number of sexual intercourse attempts, and IIEF item 15 reflects the confidence to get and maintain an erection.

IIEF = International Index of Erectile Dysfunction; IIEF-EF = IIE-Erectile Function domain score; IIEF-IS = IIEF-Intercourse Satisfaction domain score; IIEF-OS = IIEF-Overall Satisfaction domain score; IIEF-SD = IIEF-Sexual Desire domain score; nsRP = bilateral nerve-sparing radical prostatectomy; NSS = nerve-sparing score; OaD = once a day; PRN = on demand; rTx = randomized treatment.

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Table 1

Patient and disease characteristics (intention-to-treat population)

	Tadalafil 5 mg OaD (n = 139)	Tadalafil 20 mg PRN (n = 142)	Placebo (n = 141)	Overall (n = 422)
Age, yr				
Mean (SD)	58.6 (5.07)	57.6 (5.74)	57.6 (5.69)	57.9 (5.52)
Age group, n (%)				
<61 yr	82 (59.0)	84 (59.2)	91 (64.5)	257 (60.9)
61–68 yr	57 (41.0)	58 (40.8)	50 (35.5)	165 (39.1)
Ethnicity, n (%)				
White	137 (98.6)	140 (98.6)	138 (97.9)	415 (98.3)
Other ^a	2 (1.4)	2 (1.4)	3 (2.1)	7 (1.7)
BMI, kg/m ²				
Mean (SD)	26.6 (2.97)	26.8 (2.93)	27.1 (3.08)	26.9 (2.99)
nsRP approach, n (%)				
Open surgery	68 (48.9)	65 (45.8)	56 (39.7)	189 (44.8)
Conventional laparoscopy	29 (20.9)	31 (21.8)	28 (19.9)	88 (20.9)
Other surgery ^b	11 (7.9)	6 (4.2)	13 (9.2)	30 (7.1)
Robot-assisted laparoscopy	31 (22.3)	40 (28.2)	44 (31.2)	115 (27.3)
Total NSS after prostatectomy, ^c categorized, n (%)				
Perfect: 2	117 (84.2)	115 (81.0)	113 (80.1)	345 (81.8)
Not perfect: >2	22 (15.8)	27 (19.0)	28 (19.9)	77 (18.2)
IIEF domain scores at baseline (visit 1, before nsRP), mean (SD)				
IIEF Erectile Function (range: 1–30)	28.5 (1.69)	28.2 (2.52)	28.4 (1.98)	28.4 (2.09)
IIEF Orgasmic Function (range: 0–10)	9.5 (1.00)	9.4 (1.26)	9.6 (1.05)	9.5 (1.11)
IIEF Sexual Desire (range: 2–10)	7.8 (1.43)	7.8 (1.53)	9.6 (1.05)	7.7 (1.27)
IIEF Intercourse Satisfaction (range: 0–15)	11.9 (2.09)	11.7 (2.14)	11.9 (1.96)	11.8 (2.06)
IIEF Overall Satisfaction (range: 2–10)	8.7 (1.61)	8.7 (1.39)	8.9 (1.31)	8.7 (1.44)

BMI = body mass index; IIEF = International Index of Erectile Dysfunction; nsRP = bilateral nerve-sparing radical prostatectomy; NSS = nerve-sparing score; OaD = once a day; PRN = on demand; SD = standard deviation.

^aOther ethnicities included American Indian/Alaska native, Asian, and black/African American.

^bOne center using endoscopic extraperitoneal radical prostatectomy in 30 patients documented as “other surgery.”

^cSurgeons assigned an NSS between 1 and 4 for each neurovascular bundle (left and right; 1 = complete preservation, 4 = complete resection). A total NSS of 2 was considered perfect, and any total NSS >2 was considered not perfect [6].