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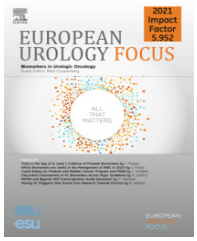

Prostate Cancer

Urinary Incontinence and Sexual Function After the Introduction of NeuroSAFE in Radical Prostatectomy for Prostate Cancer

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Abstract

Background: Nerve-sparing (NS) radical prostatectomy (RP) results in better functional outcomes. Intraoperative neurovascular structure–adjacent frozen section examination (NeuroSAFE) significantly increases the frequency of NS surgery. The effect of NeuroSAFE on postoperative erectile function (EF) and continence is not yet clear.
Objective: To describe EF and continence outcomes for men undergoing RP with the NeuroSAFE technique.
Design, setting, and participants: Between September 2018 and February 2021, 1034 men underwent robot-assisted RP. Data for patient-reported outcomes were collected via validated questionnaires.
Intervention: NeuroSAFE technique for RP.
Outcome measurements and statistical analysis: Continence was assessed using the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) or Expanded Prostate Cancer Index Composite short form (EPIC-26) and defined as use of 0–1 pads/d. EF was evaluated using EPIC-26 or the International Index of Erectile Function short form (IIEF-5), with data converted according to the Vertosick method and categorized. Descriptive statistics were used to asses and describe tumor characteristics and continence and EF outcomes.
Results and limitations: Of the 1034 men who underwent RP after introduction of the NeuroSAFE technique, 63% and 60% completed a preoperative and at least one postoperative questionnaire on continence and EF, respectively. Of the men who underwent unilateral or bilateral NS surgery, use of 0–1 pads/d was reported by 93% after 1 yr and 96% after 2 yr; the corresponding rates for men who underwent non-NS surgery were 86% and 78%. Overall, use of 0–1 pads/d was reported by 92% of the men at 1 yr and by

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94% at 2 yr after RP. Men in the NS group had a good or intermediate Vertosick score after RP more often than the non-NS group. Overall, 44% of the men had a good or intermediate Vertosick score at 1 and 2 yr after RP.

Conclusions: After introduction of the NeuroSAFE technique, the continence rate was 92% at 1 yr and 94% at 2 yr after RP. The NS group had a greater percentage of men with an intermediate or good Vertosick score and a higher continence rate after RP in comparison to the non-NS group.

Patient summary: Our study shows that after introduction of the NeuroSAFE technique during removal of the prostate, the continence rate among patients was 92% at 1 year and 94% at 2 years after surgery. Some 44% of the men had a good or intermediate score for erectile function 1 and 2 years after surgery.

1. Introduction

Radical prostatectomy (RP) is one of the main treatment options for men with localized prostate cancer (PCa). RP is complicated by erectile dysfunction in 20–90% of cases and by urinary incontinence in 3–16% [1,2]. Nerve-sparing surgery (NSS) results in better functional outcomes after RP [3–5]. Age, preoperative erectile function (EF), and the degree of preservation of the neurovascular bundles are associated with recovery of EF after RP [6–8]. It is well known that non-NSS leads to the worst postoperative EF, while bilateral and unilateral NSS show better results [9]. A review by Dubbelman et al. [10] revealed EF recovery rates of 31–86% after bilateral nerve-sparing RP, 13–56% after unilateral nerve-sparing RP, and 0–17% after non–nerve-sparing RP. However, the effect of unilateral or bilateral NSS on continence remains a matter of debate. A systematic review by Reeves et al. [11] showed that NSS significantly improved the continence rate by 19% up to 6 mo after RP. Continence rates at 12 mo of 84% for any nerve-sparing RP and 75% for non–nerve-sparing RP were not significantly different [11]. Two more recent large studies, which were not included in the systematic review, both reported that the degree of NSS improved continence rates by 15% at 1 yr after RP [5,12].

A relative contraindication for NSS is suspicion of extraprostatic extension (EPE) because of the higher risk of a positive surgical margin. Prediction of EPE, which is currently based on clinical stage, magnetic resonance imaging, and nomograms, is suboptimal [13] and could lead to unnecessary removal of the neurovascular bundles or to positive surgical margins. With intraoperative neurovascular structure–adjacent frozen section examination (NeuroSAFE), the surgical margin of the prostate adjacent to the neurovascular bundle is assessed during RP [14]. Several European centers have shown that implementation of the NeuroSAFE technique led to a greater number of unilateral and bilateral NSS procedures [15–18]. Although NeuroSAFE increases the rate of NSS, the effect on postoperative EF and continence is not yet clear. The first studies showed that the EF rate was 26–28% higher in the NeuroSAFE cohort in comparison to a non-NeuroSAFE cohort, with no significant difference in continence rates [16,19]. However, the sample size was small in both studies and one study did not use validated questionnaires. Since September 2018, RPs in the southwest of the Netherlands have been centralized in one high-volume center, the Anser Prostate Operation Clinic, and systematically performed by four surgeons using the NeuroSAFE technique. The Anser Prostate Operation Clinic has collected patient-reported outcomes for men undergoing RP. The aim of this study was to describe postoperative EF and continence for men undergoing RP with the NeuroSAFE technique in the Anser Prostate Operation Clinic.

2. Patients and methods

2.1. Study population

This study included patients who underwent robot-assisted RP for localized PCa at the Anser Prostate Operation Clinic (Maasstad Hospital, Rotterdam, the Netherlands) between September 2018 and February 2021. Since September 2018, eight medical centers in the Netherland collaborate within the Anser Prostate Network and RPs were performed by four dedicated surgeons from the network in the Anser Prostate Operation Clinic. The NeuroSAFE technique was offered to all patients irrespective of preoperative EF or continence. The NeuroSAFE technique was only omitted in cases of clinically established EPE or fibrotic adhesions or when the NeuroSAFE technique was unavailable. The study was approved by the institutional review board of Erasmus University Medical Center, Rotterdam (METC-2019-352) and the local ethics committee of Maasstad Hospital, Rotterdam (METC-2019-108).

2.2. The NeuroSAFE technique

The NeuroSAFE technique was performed as previously described by the Martini Klinik and the Anser Prostate Operation Clinic [14,20]. After removal of the prostate, posterolateral prostate tissue adjacent to the neurovascular bundle was dissected from the apex to the base bilaterally. The dissected tissues were inked for orientation and submitted to the pathology department for frozen section assessment. If the frozen section assessment showed tumor in the surgical margin, a partial or total secondary resection of the ipsilateral neurovascular bundle was performed, as described in our previous study [20]. A secondary resection was omitted in cases with a negative surgical margin, and, since February 2019, if the frozen section assessment showed a limited positive surgical margin, defined as a positive surgical margin on one side of $\leq$1 mm and Gleason pattern 3 (grade group 1) at most at the margin. Our previous study reported no tumor in the secondary resection if the frozen section assessment had a limited positive surgical margin [20].

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2.3. Patient-reported outcome measures

All patients received a preoperative questionnaire and postoperative questionnaires at 6 mo, 1 yr, and then annually after RP. The patients received either a paper- or digital-based survey that included validated generic, cancer-specific, and prostate-specific questionnaires. These were the International Index of Erectile Function short form (IIEF-5, paper-based), the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF, paper-based), or the Expanded Prostate Cancer Index Composite short form (EPIC-26, digital-based) [21–24]. Incontinence was recorded using the number of pads used daily according to the ICIQ-UI SF and EPIC-26 responses. EF was evaluated using the IIEF-5 and the sexual domain of EPIC-26. The IIEF-5 consists of five items evaluating EF, with response options ranging from 0 to 5 or from 1 to 5. The sexual domain of EPIC-26 consists of six items that are reported on a scale from 0 to 100. The sexual domain scores from EPIC-26 and IIEF-5 were converted using the method described by Vertosick et al. [25]. This involves taking the mean scores for questions 8a, 9, 10, 11, and 12 from EPIC-26 if at least three of these five questions were answered [25]. In the Vertosick scoring method, scores of $\leq$40 correspond to poor function, 40–59 to intermediate function, and $\geq$60 to good function. IIEF-5 scores were calculated by summing the number of points for all the questions. In the Vertosick scoring method, scores of $\leq$7 correspond to poor function, 8–16 to intermediate function, and $\geq$17 to good function [25].

2.4. Statistical analyses

Descriptive statistics were used to assess and describe patient and tumor characteristics as well as EF and continence results. Men were included if the preoperative questionnaire (baseline) and at least one postoperative questionnaire were available, regardless of whether they received adjuvant or salvage treatment. Men with a good preoperative Vertosick score were included in the analysis of EF after RP, and men with no preoperative pad use were included in the analysis of continence outcomes. Continence was defined as use of 0–1 pads/d. Statistical analyses were performed with R v4.0.5.

3. Results

After introduction of the NeuroSAFE technique in the Anser Prostate Operation Clinic in September 2018, 1034 men underwent RP, with the NeuroSAFE technique used in 987 (95.5%). A total of 648 men (62.7%) completed a preoperative and at least one postoperative questionnaire on continence, and 619 men (59.9%) completed a preoperative and at least one postoperative questionnaire on EF (Fig. 1).

The median patient age was 68 yr (interquartile range [IQR] 62–71) and median preoperative prostate-specific antigen was 9.1 ng/ml (IQR 6.2–13.4; Table 1). Clinical stage T2 or T3 was found in 53.3% of the patients and 79.3% had biopsy grade group $\geq$2. In terms of NNS, 15% did not have NNS, 30.0% had unilateral NNS, and 55.0% had bilateral NNS.

3.1. Continence

Before surgery, 624/648 men (96.3%) reported no pad use, 21 (3.2%) used one pad, and three (0.5%) used $\geq$2 pads daily. Of the 624 men with no pad use before RP, 54.5% underwent bilateral NSS and 32.4% underwent unilateral NSS (Table 2); 41.3% had pT3 and 58.7% had pT2 disease. Postoperative use of 0–1 pads/d was reported by 91.7% of the men at 1 yr and by 94.0% at 2 yr after RP. Among the men who underwent unilateral or bilateral NSS, use of 0–1 pads/d was reported by 92.6% at 1 yr and 96.1% at 2 yr after RP, compared to 85.5% and 77.8% of the men who underwent non-NSS, respectively (Fig. 2).

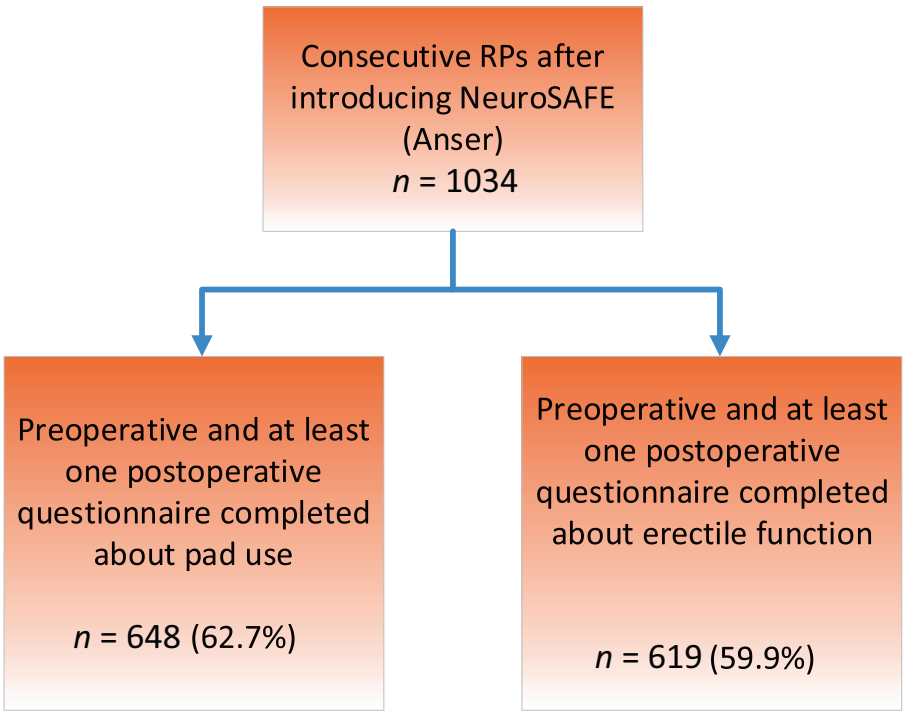

Fig. 1 – Flow diagram of men who completed questionnaires on pad use and erectile function.

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Table 1 – Patient characteristics (*n* = 1034)

Parameter	Result
Median age, yr (IQR)	68 (62–71)
Median PSA, ng/ml (IQR)	9.1 (6.2–13.5)
cT stage, *n* (%)	
cT1	483 (46.7)
cT2	392 (37.9)
cT3	159 (15.4)
Biopsy grade group, *n* (%)	
Grade group 1	214 (20.7)
Grade group 2	430 (41.6)
Grade group 3	216 (20.9)
Grade group 4	117 (11.3)
Grade group 5	57 (5.5)
D'Amico risk group, *n* (%)	
Low	113 (10.9)
Intermediate	522 (50.5)
High	399 (38.6)
Postoperative characteristics	
pT stage, *n* (%)	
pT2	603 (58.3)
pT3	431 (41.7)
RP grade group, *n* (%)	
Grade group 1	95 (9.2)
Grade group 2	521 (50.4)
Grade group 3	290 (28.0)
Grade group 4	64 (6.2)
Grade group 5	64 (6.2)
pN stage, *n* (%)	
pN0	522 (50.5)
pN1	87 (8.4)
pNx	425 (41.1)
Nerve-sparing, *n* (%)	
None	155 (15.0)
Unilateral	310 (30.0)
Bilateral	569 (55.0)
Positive surgical margins, *n* (%)	
All patients	294 (28.4)
Patients with pT2 disease	111 (18.4)
Patients with pT3 disease	183 (42.5)

IQR = interquartile range; RP = radical prostatectomy; PSA = prostate-specific antigen.

3.2. *Erectile function*

Of the men who completed the preoperative and at least one postoperative questionnaire on EF, the preoperative Vertosick score was poor for 213 (34.4%), intermediate for 104 (16.8%), and good for 302 (48.8%). Of the men with a good Vertosick score before RP, unilateral NSS was performed in 33.1% and bilateral NSS in 56.6% (Table 3). The proportion of these men with an intermediate or good Vertosick score was 43.6% at 1-yr and 45.1% at 2-yr follow-up. Men in the NSS group had a good or intermediate Vertosick score more often after RP than men in the non-NSS group (Fig. 2). For the men who completed the digital survey (EPIC-26), we looked at the individual item on the quality of erections experienced after RP. Of the men with an erection suitable for intercourse before RP, the proportion who experienced an erection suitable for intercourse after RP was 22.7% at 1 yr and 20% at 2 yr (Table 4). For men who completed the paper-based survey (IIEF-5), we looked at the individual item assessing how often erections were sufficient to achieve penetration. Of the men who indicated that they sometimes, most times, or almost always/always had erections sufficient for penetration before RP, the proportion who sometimes, most times, or almost always/always had erections sufficient for penetration after RP was 21.1% at 1 yr and 28.3% at 2 yr (Table 4).

4. Discussion

NeuroSAFE is increasingly being offered to increase the rate of NSS among men undergoing RP. Here we present patient-reported continence and EF outcomes after the introduction of the NeuroSAFE technique in the Anser Prostate Operation Clinic. At 1 yr after RP, 93% of the men who underwent unilateral or bilateral NSS used 0–1 pads/d, which increased to 96% after 2 yr. Among men who underwent non-NSS, 86% used 0–1 pads/d after 1 yr, which decreased to 78% after 2 yr. Of the men with a good Vertosick score before RP, the proportion with a good or intermediate Vertosick score at 1 yr after RP was 49% in the bilateral NSS, 43% in the unilateral NSS, and 15% in the non-NSS group.

Preservation of the neurovascular bundle can reduce the postoperative rate of erectile dysfunction and possibly incontinence [3–5,9,12]. In our study we observed better EF and continence rates for men who had any NSS in com-

Table 2 – Preoperative and postoperative results for patients with no pad use preoperatively

	Preoperative (*n* = 624)	6 mo (*n* = 419)	1 yr (*n* = 408)	2 yr (*n* = 232)
Pad use, *n* (%)				
0 pads/d	624 (100.0)	208 (49.6)	245 (60.0)	143 (61.6)
1 pad/d	0 (0.0)	157 (37.5)	129 (31.6)	75 (32.3)
≥2 pads/d	0 (0.0)	54 (12.9)	34 (8.3)	14 (6.0)
Median age, yr (IQR)	68 (63–71)			
pT stage, *n* (%)				
pT2	366 (58.7)	251 (59.9)	241 (59.1)	137 (59.1)
pT3	258 (41.3)	168 (40.1)	167 (40.9)	95 (40.9)
RP grade group, *n* (%)				
Grade group 1	56 (9.0)	40 (9.5)	37 (9.1)	15 (6.5)
Grade group 2	324 (51.9)	228 (54.4)	219 (53.7)	125 (53.9)
Grade group 3	176 (28.2)	105 (25.1)	103 (25.2)	69 (29.7)
Grade group 4	32 (5.1)	23 (5.5)	23 (5.6)	11 (4.7)
Grade group 5	36 (5.8)	23 (5.5)	26 (6.4)	12 (5.2)
Nerve-sparing, *n* (%)				
None	82 (13.1)	50 (11.9)	55 (13.5)	27 (11.6)
Unilateral	202 (32.4)	144 (34.4)	130 (31.9)	82 (35.3)
Bilateral	340 (54.5)	225 (53.7)	223 (54.7)	123 (53.0)

IQR = interquartile range; RP = radical prostatectomy.

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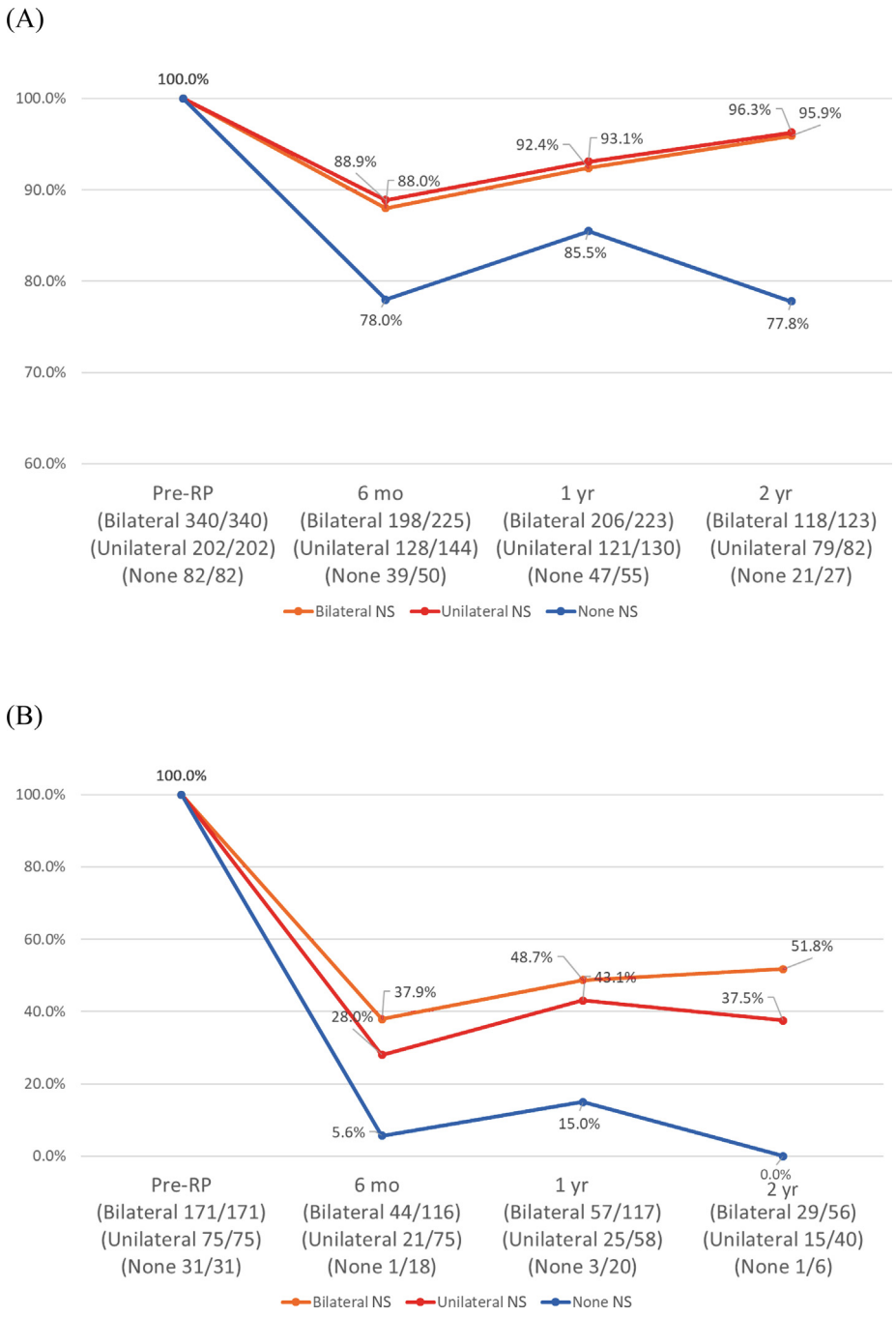

Fig. 2 – Erectile function and continence outcomes by degree of nerve-sparing (NS) during radical prostatectomy (RP). (A) Patients reporting use of 0–1 pads/d after RP. (B) Patients reporting a good or intermediate Vertosick score for erectile function after RP.

parison to men with non-NSS, which is in line with previous studies [4,5,8,9]. The number of men experiencing acceptable EF varies widely because of heterogeneity in study populations, patient age, and surgeon experience [3–5,7,8,10,26]. However, studies have shown that bilateral NSS leads to the best postoperative EF and non-NSS to the worst postoperative EF. The effect of NSS on post-RP continence is more debatable. In a review by Reeves et al. [11], 84% of the NSS cohort reported that they were continent after 1 yr versus 75% of the non-NSS cohort, but this difference was not significant. Two large and more recent studies reported better continence recovery for the NSS groups than for the non-NSS groups [5,12]. Furthermore, Suardi et al. [4] reported a continence rate of 80% for bilateral NSS, 63% for unilateral NSS, and 45% for non-NSS after 1 yr. On the basis of the above-mentioned studies and our data, NSS seems to improve functional outcomes after RP. Moreover, previous studies showed that the NeuroSAFE technique significantly increased the rate of NSS procedures; bilateral and unilateral NSS increased by 1–30% in the pT2 setting and by 17–49% in the pT3 setting [15–18]. We thus postulate that as NeuroSAFE increases the rate of NSS procedures and that

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Table 3 – Preoperative and postoperative results for patients with a good preoperative Vertosick score

	Preoperative (n = 302)	6 mo (n = 209)	1 yr (n = 195)	2 yr (n = 102)
Vertosick score, n (%)				
Poor	0 (0.0)	143 (68.4)	110 (56.4)	57 (55.9)
Intermediate	0 (0.0)	49 (23.4)	38 (19.5)	20 (19.6)
Good	302 (100.0)	17 (8.1)	47 (24.1)	25 (24.5)
Median age, yr (IQR)	66 (61–70)			
pT stage. n (%)				
pT2	174 (57.6)	127 (60.8)	117 (60.0)	63 (61.8)
pT3	128 (42.4)	82 (39.2)	78 (40.0)	39 (38.2)
Gleason grade group, n (%)				
Grade group 1	33 (10.9)	22 (10.5)	20 (10.3)	9 (8.8)
Grade group 2	158 (52.3)	119 (56.9)	108 (55.4)	58 (56.9)
Grade group 3	71 (23.5)	39 (18.7)	38 (19.5)	23 (22.5)
Grade group 4	17 (5.6)	16 (7.7)	15 (7.7)	7 (6.9)
Grade group 5	23 (7.6)	13 (6.2)	14 (7.2)	5 (4.9)
Nerve-sparing, n (%)				
None	31 (10.3)	18 (8.6)	20 (10.3)	6 (5.9)
Unilateral	100 (33.1)	75 (35.9)	58 (29.7)	40 (39.2)
Bilateral	171 (56.6)	116 (55.5)	117 (60.0)	56 (54.9)

IQR = interquartile range.

Table 4 – Preoperative and postoperative questionnaire results for erection quality

	Patients, n (%)			
	Preoperative	6 mo	1 yr	2 yr
EPIC-26: How would you describe the usual quality of your erections during the last 4 wk?	(n = 107)	(n = 86)	(n = 88)	(n = 20)
1. None at all	0	31 (36.0)	24 (27.3)	5 (25.0)
2. Not firm enough for any sexual activity	0	26 (30.2)	16 (18.2)	6 (30.0)
3. Firm enough for masturbation and foreplay only	0	19 (22.1)	28 (31.8)	5 (25.0)
4. Firm enough for intercourse	107 (100.0)	10 (11.6)	20 (22.7)	4 (20.0)
IIEF-5: How often were your erections hard enough for penetration?	(n = 214)	(n = 127)	(n = 118)	(n = 92)
0. No sexual activity	0	25 (19.7)	31 (26.3)	27 (29.3)
1. Almost never/never	0	73 (57.5)	50 (42.4)	32 (34.8)
2. A few times (much less than half the time)	0	18 (14.2)	12 (10.2)	7 (7.6)
3. Sometimes (about half the time)	35 (16.4)	4 (3.1)	9 (7.6)	8 (8.7)
4. Most times (much more than half the time)	42 (19.6)	3 (2.4)	9 (7.6)	10 (10.9)
5. Almost always/always	137 (64.0)	4 (3.1)	7 (5.9)	8 (8.7)

EPIC = Expanded Prostate Cancer Index Composite; IIEF = International Index of Erectile Function.

NSS decreases the risk of incontinence and erectile dysfunction, use of the NeuroSAFE technique could improve functional outcomes after RP.

In our study, the overall continence rate was 92% at 1 yr and 94% at 2 yr after RP, which is similar to the rates reported by Noël et al. [27] and Mirmilstein et al. [16], but slightly lower than the rates reported by Fosså et al. [19] (NeuroSAFE cohort: 84% no pad used, non-NeuroSAFE cohort: 75% no pad use).

After introduction of the NeuroSAFE technique in the Anser Prostate Operation Clinic, 43.6% of men reported a good or intermediate Vertosick score at 1 yr and 44.1% at 2 yr after RP. Mirmilstein et al. [16] only described EF for men who underwent NSS (unilateral or bilateral) and showed that EF rates improved by 26–31% when the NeuroSAFE technique was used. Noël et al. [27] reported that 12% of men who underwent RP with the NeuroSAFE technique had spontaneous erections after RP, 27% had erections with PDE-51, and 30% had partial erections. Fosså et al. [19] found that 66% of men who underwent RP with the NeuroSAFE technique had good EF at or after 12 mo. It should be noted that in the studies by Mirmilstein et al, Noël et al, and Fosså et al, a greater proportion of the men who underwent RP with the NeuroSAFE technique had pT2 disease in comparison to our study, and Mirmilstein et al. and Fosså et al. only described the EF rate for men undergoing NSS [16,19,27]. Mirmilstein et al. [16] and Noël et al. [27] derived EF data from follow-up consultations recorded by the surgeon, while Fosså et al. [19] and our study used validated questionnaires. Age also has a strong association with EF recovery [8] and our study population was older. Men in our cohort had a median age of 68 yr, while the other study populations included men aged 58–61 yr [16,19,27].

A Dutch observational study evaluated incontinence and erectile dysfunction after RP in daily clinical practice using a nationwide cohort [26]. Use of 0–1 pads/d was reported by 79% of the patients at 1 yr and by 85% at 2 yr after RP. Erectile dysfunction was based on one question from EPIC-26 and defined as erections that were not suitable for sexual intercourse. Erectile dysfunction was reported by 93% of the men at 1 yr and by 87% at 2 yr after RP. The rates of postoperative continence and EF reported in the current study seem to be higher than those reported by Vernooij et al. [26] for nationwide daily clinical practice in the Netherlands.

To the best of our knowledge, this is the largest prospective study evaluating functional outcomes of the NeuroSAFE

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technique using validated questionnaires in daily clinical practice. We provided detailed information on continence and EF outcomes for men who underwent robot-assisted RP after introduction of the NeuroSAFE technique. An important limitation of this study is the limited response rate; only 60% of the men completed the preoperative and at least one postoperative questionnaire on erectile function and 63% of the men about continence. Another limitation is that no direct comparison with men who underwent RP without the NeuroSAFE technique was possible. Centralization of RP (four surgeons performed all RPs in the Anser Prostate Operation Clinic) may also have contributed to the functional outcomes experienced and reported after RP. However, we did observe that overall, a good or intermediate Vertosick score after RP was more frequent in the NSS group than in the non-NSS group. Moreover, two different validated questionnaires were used to measure EF. This was resolved by applying the Vertosick method to convert sexual domain scores from EPIC-26 and IIEF-5 to a common scale (poor, intermediate, or good EF). Future efforts within the Anser Prostate Cancer Network should focus on increasing the response rate. By incorporating patient-reported outcomes in the PCa care path, both urologists and patients will be more aware of patient values and preferences regarding PCa treatment, which may enhance informed and shared decision-making.

5. Conclusions

In conclusion, our study shows that after introduction of the NeuroSAFE technique for RP, postoperative continence rates were high, at 92% at 1 yr and 94% at 2 yr after RP. Furthermore, 44% of patients had good or intermediate EF at 1 or 2 yr after RP. NSS resulted in better rates of continence and EF, and use of the NeuroSAFE technique improves NSS, especially in men with T3 disease. We therefore postulate that use of the NeuroSAFE technique could improve functional outcomes after RP.

Author contributions: Lionne D.F. Venderbos had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: van der Slot, Busstra, Gan, Klaver, Rietbergen, den Bakker, Kweldam, Venderbos, Anser Prostate Cancer Network.
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