Improved patient-reported functional outcomes after nerve-sparing radical prostatectomy by using NeuroSAFE technique

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Running head: Improved functional outcomes after NeuroSAFE

Key words: Nervesparing prostatectomy; Frozen sections; Adverse health outcomes; EPIC-26

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ABSTRACT

Purpose: To explore whether prostatectomized men report improved post-operative erectile function and urinary control dependent on the application of intra-operative frozen section examination (NeuroSAFE) during nerve-sparing radical prostatectomies (NS-RPs).

Methods: Pre-and post-RP responses to the sexual domain and the urinary incontinence subscale of EPIC-26 were analyzed in 95 and 312 men from a NeuroSAFE Group (Martini-Klinik, Hamburg, Germany) and a Non-NeuroSAFE Group (Oslo University Hospital, Norway), undergoing NS-RPs for $\leq$ cT2 prostate cancer. All patients had intra-prostatic tumors as evaluated by Digital Rectal Examination. Statistical significance in bivariate and multi-variable analyses: $p < 0.05$.

Results: With similar oncological outcomes and not associated with the performance of bilateral or unilateral NS-RP within each group patients from the NeuroSAFE Group had better sexuality outcomes than those from the NonNeuroSAFE Group ($p < 0.01$). Age and pre-RP sexual function represented significant co-variables. In pre-RP potent men, erectile function was preserved in 74% men of the NeuroSAFE Group and in 46% in those from the NonNeuroSAFE Group ($p < 0.01$). Any superior continence- saving effect of NeuroSAFE was limited.. The non-randomized small-sized observational study design represents the observations' main limitation.

Conclusions: Our study indicates that NeuroSAFE contributes to preservation of post-RP erectile function. If confirmed in a randomized trial the NeuroSAFE should be applied in patients undergoing NS-RP for maximal preservation of post-RP sexual function.

Introduction (1998 words)

Post-prostatectomy loss of erectile function and urinary leakage represent feared long-term post-prostatectomy adverse health outcomes (AHOs) in many men with prostate cancer (PCa). Preservation of the neurovascular bundle (NVB) by nervesparing (NS) reduces this risk, but must be balanced against the incidence of positive surgical margins (PSMs) [1-4]. Though still debated, intra-operative frozen-section examination of the resection margins may increase the chance to restrict the dissection to the intra-or inter-fascial plane without compromising the oncological outcome [5-7]. At the Martini-Klinik (MK), the NeuroSAFE approach has been developed which combines NS with intra-operative neurovascular structure-adjacent frozen section examination [8,9]. Applying NeuroSAFE, Mirmilstein et al [10] have reported functional and short-term oncological results which supersede those after conventional NS.

Since 2013 Norwegian men have opted to undergo a NeuroSAFE-based RP at the MK, expecting fewer post-RP AHOs than published from Norway [11,12,13]. Presently it is unknown whether expectations are fulfilled. The present retrospective observational study therefore asks the question:

Do statistically significant differences exist for post-RP erectile dysfunction and urinary incontinence between patients who have undergone NS at MK or Oslo University Hospital (OUH) after adjusting for medical and psycho-social co-variables?

Methods

Patients:

From 2013 to 2016, 305 Norwegian men underwent NS with the NeuroSAFE technique at the MK (*NeuroSAFE Group*). We identified 437 men who during the same period had “conventional” NS at OUH (*NonNeuroSafe Group*). After approval by the OUH’s Data Protection Office the above patients were in 2018 invited to participate in a questionnaire-based survey which explored their post-RP AHOs. The present analyses are restricted to men who, based on Digital Rectal Examination (DRE), presented with intra-prostatic tumors and in whom comparable pre- and post-treatment treatment questionnaires were available. The questionnaire contained the Norwegian version of EPIC-26 [14], the SF12 quality of life questionnaire [15] and questions as to individual medical and psycho-social features. The questionnaire also assessed post-RP oncological treatment (pelvic radiotherapy, hormone therapy) and the latest level of PSA. Marital status was dichotomized (paired versus single). Psycho-social variables covered educational status (high school or less versus college/university), the patient’s latest profession (chairmen/academics versus employees within office/service/sales versus farmers/ fishermen/ craftsmen) and current daily cigarette smoking (yes /no). Co-morbidity identified the number of chronic diseases impacting on daily activity (0 versus ≥ 1). Self-rated general health from the SF12 form was dichotomized (Good: Excellent/Very good/Good versus Fair/Poor). The patient also recorded use and effectiveness (yes/no) of oral or urethral pro-erectile aids. The Type D Scale-14 [16] described the patient’s personality covering negative affectivity (dysphoria, worry, irritability) and social

inhibition (discomfort in social interactions). A Type D1 personality reflects a man's likelihood to respond with increased anxiety and depression to stressful life situations.

Primary outcomes were the post-RP Sexual Summary Score (SexSS) and the post-RP Urinary Incontinence SubScale (UrInSS) of EPIC-26, ranging from 0 (worst) to 100 (best) (Cronbach alpha: 0.79 -0.93). Secondly the patient reported the effect of PDE5Is : Without considering the effect of erectile aids "Erectile dysfunction" was defined by patients' dichotomized response to Item 10 of EPIC- 26 indicating that "erection was never achieved or in less than half of the occasions when it was wanted". "Pad use" was dichotomized (0 versus ≥ 1 pad). Medical data were abstracted from hospital registries.

Evaluable patients finally fulfilled the following criteria:

1. Available pre- and post RP EPIC-26
2. No extra-prostatic extension by DRE
3. No previous pelvic surgery or pelvic radiotherapy
4. No pre-operative hormone therapy
5. Identifiable risk group [17]

Statistics

Descriptive statistics were presented as numbers and percentages for categorical data and as medians with ranges for continuous data. Inter-group comparisons were performed by chi-square test and Mann-Whitney test. Multivariable linear and logistic regressions were performed to assess the association between NeuroSAFE treatment and post-RP outcomes, including available pre-RP variables. Results were presented as beta coefficients or odds ratios (OR) with accompanying 95% confidence intervals. No multicollinearity or interactions effects were observed. All tests were two-sided setting the level of statistical significance to <0.05 . Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 24.0. [18] and Stata, Release 15 [19].

Results

Patients:

The final cohort comprised 95 and 312 patients from respectively the NeuroSAFE and NonNeuroSAFE Group. (Figure1) All patients in the NonNeuroSafe group and 88 men in the NeuroSAFE Group had undergone robotic-assisted laparoscopic prostatectomy with longer follow-up since RP in the former group. ($p:0.005$; Table 1A) Bilateral NS was done in 79% of the patients in the NeuroSAFE Group, compared to 29% in the NonNeuroSAFE Group (Table 1A). The distribution of clinical risk groups was similar in both groups. No significant inter-group differences emerged for the frequency of pT3 disease, PSM, post-operative oncological treatment or post-RP PSA-levels of ≥ 0.5 ng/ml.

Patients from the NeuroSAFE Group were younger than those from the NonNeuroSAFE Group ($p=0.005$; Table 1B). The educational level, co-morbidity and indicators of the patient's psycho-social situation (Marital status, profession, smoking, personality) were similarly distributed between the two groups.

Sexuality/urinary function

In bivariate analyses significantly lower figures emerged in the Non-NeuroSAFE Group for the variables assessing post-treatment sexuality ($p \leq 0.01$; Table 2), with inter-group differences as to uni- and bilateral NS. Sixty-six % of men from the NeuroSAFE Group post-operatively reported “no ED” compared to 36% from the NonNeuroSAFE Group. After RP with the NeuroSAFE technique 83% of the men reported effective use of pro-erectile aids compared to 50% of men operated without this approach at OUH. . Also the post- RP UrInSS differed between the two groups ($p:0.03$), with marginally significant difference concerning post-RP pad use ($p:0.06$).

Favorable outcomes in the NeuroSAFE Group were maintained if analyses were restricted to patients who pre-operatively had no ED, did not use pads and had no post-RP oncological therapy (Figure 2). Most post-RP figures for sexual outcomes for the NonNeuroSAFE Group were significantly inferior to those from the NeuroSAFE Group. No significant inter-group differences emerged for urinary function.

Multi-variable analyses

Sexuality: In multi-variable analyses the sexuality outcomes were significantly more favorable after the NeuroSAFE method than after the Non-NeuroSAFE ($p < 0.01$; Table 3A) with age, pre-treatment SexSS, pre-treatment erectile function and a high-risk PCa being significant co-factors. Patients from the NonNeuroSAFE Group had an about three-fold increased risk for post-RP ED compared to men from the NeuroSAFE Group, their chance for favorable response to pro-erectile aids being reduced by about 75%.

Urinary function: The level of pre-RP UrInSS and being single remained associated with post-RP UrInSS (respectively $p < 0.01$ and $p = 0.02$; Table 3B) with older age increasing the pad use ($p = 0.06$).

The performance of unilateral or bilateral nerve-sparing RP was not associated with any of the selected outcomes.

Discussion

This is the first study ever published which in patients with $\leq cT2$ PCa evaluates post-RP outcomes after NeuroSafe-assisted nerve-sparing RP applying pre- and post-RP EPIC-26 questionnaires. Patients prostatectomized with the NeuroSAFE method had significantly better sexuality outcomes than those undergoing nerve-sparing RP without this approach. Age, pre-treatment sexuality-related variables and presenting with a high-risk tumor were significant co-variables. The level of pre-RP UrInSS, , was positively associated with post-RP UrInSS with “being single” decreasing this outcome. No significant outcome differences emerged between bilateral or unilateral nerve-sparing.

The introduction of NS has resulted in some improvement of post-RP recovery of erectile and urinary function [1-4], in particular if done intra-fascially [20,21] but , and in agreement with our study without clear differences between unilateral and bilateral NS . Further, NS increases the chance for favorable response to pro-erectile aids [22], this effect in our study enhanced by NeuroSAFE. Recent findings from an American high-volume center suggest that, despite the advancements in surgical and postoperative care, the hospital’s overall post-

RP erectile function outcomes have not improved [23]. and that additional strategies are required to improve post-RP recovery of erectile function. The NeuroSAFE procedure may represent such a strategy. We confirm previous observations that this strategy can be applied in patients with high risk tumors without increasing the risk of tumor-positive margins [3,6,10]. Application of NeuroSAFE will thus increase the number of patients in whom NS is a safe treatment option (24). In our study we are the individual patient unaware of the extent of NS (inter-versus intrafascial NS). The intra-fascial approach guided by NeuroSAFE is, however, the principal routine at the MK. At the OUH only approximately 10% of nervesparing RPs are intra-fascial procedures. Together with the significant age difference this may explain that post-RP potency is preserved in only 46% of the pre-operatively potent patients from the NonNeuroSAFE Group compared to 74% after the NeuroSAFE approach.

Our comparative study confirms Mirmilstein et al [10] findings as to the potency-saving effect of NeuroSAFE as compared to NS without this approach, whereas the continence-saving effect of the NeuroSAFE method was limited. Interestingly, our figure for post-RP use of “no pad” is in the NeuroSAFE Group lower (84%) than reported (95%) from the MK [25]. Introduction of the NeuroSAFE method increases costs, especially for the pathological department. Such expenses must, however, be balanced against reduction of positive surgical margins, of urinary incontinence and of erectile dysfunction resulting in fewer salvage therapies and reduced need for erectile aids/rehabilitation tasks.

Results from our comparative study as to the importance of age and pre-RP function are in agreement with Salonia et al's [20] view that post-RP outcomes depend on the selection of the right patients. These co-factors must be considered if inter-group differences of AHOs are analyzed. Further, recent studies have documented that PCa patients with pre-RP mental distress and/or those from low social classes report more post-RP AHOs than those without these characteristics [24-29]. The association between these non-surgical background conditions (depression, anxiety, educational level) and post-RP outcomes may be particularly obvious when AHOs are assessed by self-report as done by EPIC-26, covering both functional and bother items. In our study the variables reflecting a patient's socio-economic condition and mental health (“type D1 personality”) were similarly distributed across the two groups. Except for age and “being single” they were neither associated with the selected AHOs, admittedly based on few patients. The shown inter-group outcome differences are therefore not explained by these non-surgical characteristics.

Our study emphasizes that any inter-group comparison of post-RP AHOs requires adjustments age, co-morbidity, risk groups together with pre-treatment sexual and urinary function. Lack of such background information, not always evident in the lay press dealing with post-RP AHOs, leads to unjustifiable comparisons..

Finally, in most reports the percentages of post-RP AHOs are related to the pT category, whereas pre-RP counseling as to the risk of post-RP AHOs must consider the extension and aggressiveness of the disease as evident before RP. Our main analyses are therefore based on pre-operatively identified risk groups, admitting the limited diagnostic accuracy of DRE.

Limitations and Strengths

Small sample is this study's main limitation, together with the fact that the retrospective observational design can not consider all possibly important selection bias.

Further, we do not have information about each patient's pre-and post-RP rehabilitation tasks for recovery of potency and urinary control. Nor can we estimate inter-surgeon expertise variability or any relation of the patient-reported outcomes to the performance of inter-versus intrafascial nervesparing. Finally, the analysis is restricted to patients with $\leq$ cT2 tumors, though nerve-sparing RP also may have a place in patients with locally more advanced PCa. The fact that patients from both groups are operated contemporarily during recent years is viewed as an advantage. The pre- and post-RP use of the internationally recommended EPIC-26 instrument is also considered as strength. All patients are operated at hospitals with long-term experience with RP and more than 100 RPs annually per urologist, though the numerically larger experience at the Martini Hospital is acknowledged.

Conclusion

In patients with $\leq$ cT2 PCa preservation of post-RP potency is approximately doubled in patients operated with NeuroSAFE-based RP compared to patients undergoing nervesparing RP without this approach, reflected by more favorable sexual summary scores of EPIC-26. Between group-differences as to post-RP urinary control are more limited. Our findings from this retrospective observational study have to be confirmed in a randomized trial, which also should include patients with extraprostatic tumors.

Ethical considerations: The performance of the study was approved by the Oslo University Hospital's Data Protection Office. All patients provided written consent to participate in the study.

Authors' contribution:

S.D. Fosså: Project development, Data collection, Manuscript writing, Prof.em. Oncologist

B. Beyer: Data collection, Manuscript editing, Urologist

A.A. Dahl: Project development, Manuscript editing, Research Consultant, Psychiatrist

L.M. Eri: Data collection, Prof. Urologist

E. Kvan: Project development, Urologist

R.S. Falk: Data analysis, Statistician

M. Graefen: Project development, Manuscript editing; Urologist, Initiator of NeuroSAFE

H. Huland: Project development, Urologist, Head of the Dep.of Urology at Martini-Klinik

V. Berge: Project development, Data collection, Manuscript writing, Urologist

Conflict of interest: None for any of the authors.

Funding details: The study was financially supported by The Radium Hospital Foundation Project number 335007.

Acknowledgement: We thank Vigdis Oppenud for support during finalizing the manuscript.

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Legends for Figures:

Figure 1: Consort diagram: Patients with nerve-sparing radical prostatectomy (2013-2016) at Martini Klinik (NeuroSAFE Group) or Oslo University Hospital (Non-NeuroSAFE Group)

Figure 2: Post-RP patient-reported outcomes after nerve-sparing RP with or without NeuroSAFE in patients without erectile dysfunction and no use of pads before RP and no post-RP hormones/radiotherapy .

A: Sexual Life: **Left panels:** Medians of EPIC- 26 Sexual Summary Scores; **Central panels** :% of patients with No Erectile Dysfunction; **Right panels:** % of patients with effect of PDE5Is

B: Urinary continence :**Left panel:** Medians of EPIC-26 Urinary Incontinence Scores ; **Right panel:** % patients with no use of pads.

NeuroSAFE Group (Bilateral nerve-sparing: n:62; Unilateral nerve-sparing: n:12; Median age:61 years [47-75])

NonNeuroSAFE Group (Bilateral nerve-sparing: n:67; Unilateral nerve-sparing: n:149; Median age:64 years [44-75])

Figure 1: Consort diagram: Patients with nerve-sparing radical prostatectomy (2013-2016) at Martini Klinik (NeuroSAFE Group) or Oslo University Hospital (Non-NeuroSAFE Group)

¹ No pre-RP questionnaires available, mainly due to linguistic problems for most of the Norwegian patients at the Martini Hospital; ²Number of patients without post-RP radiotherapy/hormone treatment

Figure 2: Post-RP patient-reported outcomes after nerve-sparing RP with or without NeuroSAFE in patients without erectile dysfunction and no use of pads before RP and no post-RP hormones/radiotherapy .

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■ NonNeuroSAFE Group (Bilateral nerve-sparing: n:67; Unilateral nerve-sparing: n:149; Median age:64 years [44-75])

A: Sexual life

Bilateral nerve-sparing

Unilateral nerve-sparing

Any nerve-sparing

B:Urinary continence : **Left panel:** Medians of EPIC-26 Urinary Incontinence Scores ;
Right panel: % patients with no use of pads.

Bilateral nerve-sparing

Unilateral nerve-sparing

Any nerve-sparing

**Median Urinary
Incontinence score**

No use of pads

Table 1 A: Medical variables and post-RP oncological outcome B:Socio-demographic variables

Variable	NeuroSAFE Group (n=95)	Non-NeuroSAFE Group (n=312)	p-value
Medical variables			
Years since RP ¹	2.6 (1.4-3.4) [0.84]	2.7 (1.5-5.7) [1.05]	0.005
Risk groups ²			
Low	9 (10%)	31 (10%)	0.99
Intermediate	69 (73%)	227 (73%)	
High	17 (18%)	54 (17%)	
Nerve- sparing			<0.001
Bilateral	75 (79%)	90 (29%)	
Unilateral	20 (21%)	222 (71%)	
Tumor-positive margins			
ALL	11 (12%)	53 (17%)	0.20
pT2	6/67 (9%)	12/159 (8%) ⁴	0.76
pT3	5/28 (18%)	39/141 (28%) ⁴	0.28
Oncological outcome			
Post-RP			
Hormones/Radiotherapy	13 (14%)	49 (16%)	0.63
Current PSA ≥0,5 ng /ml ³	5 (5%)	27 (9%)	0.28

¹Median (range)[interquartile range]; ²D'Amico groups (17); ³Restricted to patients without post-RP hormones

B

Variable	NeuroSafe Group (n=95)	Non-NeuroSAFE Group (n=312)	p-value
Age at RP(years) ¹	61 (47-75)	64 (44-75)	0.005
<50	5 (5%)	8 (3%)	
50-59	30 (32%)	78 (25%)	
60-69	52 (55%)	193 (62%)	
≥70	8 (8%)	33 (11%)	
Co-morbidity ≥1 Chronic disease ²	12 (13%)	39 (13%)	0.97
General health			0.78
Good	87 (92%)	280 (91%)	
Impaired	8 (8%)	29 (9%)	
Civil status			0.18
Single	7 (7%)	38 (12%)	
Education			0.10
High	65 (68%)	182 (59%)	
Medium/Low	30 (32%)	127 (41%)	
Profession			0.31
Chairmen/ Academics	62 (70%)	175 (65%)	
Office/Sale/Service	19 (22%)	55 (21%)	
Farmer/Fishermen/Craftsmen	7 (8%)	38 (14%)	
BMI			0.37
Pre-RP ¹	26 (20-36)	26 (20-58)	
Current smoker	5 (5%)	24 (8%)	0.42
Type D personality ³	7 (7%)	39 (13%)	0.16

¹Median (range); ²With impairment of daily activities; ³(ref.1

Table 2: Pre- and post-treatment key variables**PRE-treatment**

	NeuroSAFE Group			Non-NeuroSAFE Group			p-values		
	Bilateral (75)	Unilateral (20)	All (95)	Bilateral (90)	Unilateral (222)	All (312)	Bilateral¹	Unilateral¹	All¹
Sexual summary score (SexSS)	83 (14-100)	83 (28-100)	83 (14-100)	83 (4-100)	75 (0-100)	79 (0-100)	0.59	0.12	0.002
# potent patients ²	70 (95%)	19 (95%)	89 (95%)	80 (90%)	180 (83%)	260 (85%)	0.27	0.15	0.01
Urinary Incontin. SubScale (UrInSS)	100 (44-100)	100 (54-100)	100 (44-100)	100 (54-100)	100 (40-100)	100 (40-100)	0.42	0.91	0.34
No pad use ²	73 (97%)	20 (100%)	93 (98%)	90 (100%)	215 (97%)	305 (98%)	0.12	0.42	0.94

POST-treatment

	NeuroSAFE Group			Non-NeuroSAFE Group			p-values		
	Bilateral (75)	Unilateral (20)	All (95)	Bilateral (90)	Unilateral (222)	All (312)	Bilateral¹	Unilateral¹	All¹
Sexual summary score (SexSS)	61 (0-100)	57 (4-96)	61 (0-100)	34 (0-100)	27 (0-100)	31 (0-100)	<0.001	0.005	<0.001
# potent patients ²	50 (67%)	13 (65%)	63 (66%)	35 (39%)	77 (35%)	112 (36%)	<0.001	0.007	<0.001
Effect of erectile aids	48/58 (83%)	14/17 (82%)	62/75 (83%)	32/59 (54%)	59/124 (48%)	91/183 (50%)	0.001	0.007	<0.001
Urinary Incontin. SubScale (UrInSS)	94 (31-100)	89 (17-100)	94 (17-100)	90 (8-100)	86 (0-100)	86 (0-100)	0.15	0.52	0.03
No pad use ²	63 (84%)	17 (85%)	80 (84%)	72 (80%)	162 (73%)	234 (75%)	0.51	0.24	0.06

¹ Comparisons between indicated subgroups for the NeuroSAFE Group vs the NonNeuroSAFE Group² Percentages are based on valid responses , with shown denominator for selected variables.

Table3: Multi-variable analyses: Post-RP sexuality (A) and urinary incontinence (B) outcomes restricted to 345 patients without subsequent radiotherapy/hormones

A	Sexual Summary Score (SexSS ¹) (n=340)			Erectile Dysfunction (n=335)			Effective Pro-erectile Aids (n=215)		
	β	95% CI. ²	p	OR	95% CI.	p	OR	95% CI.	p
Treatment									
NeuroSAFE	Ref			Ref			Ref		
Non-NeuroSAFE	-18.3	-28.9; -7.7	0.001	3.12	1.59; 6.11	0.001	0.20	0.08; 0.48	<0.001
Nerve sparing									
Unilateral	Ref			Ref			Ref		
Bilateral	-5.0	-14.4; 4.4	0.29	1.11	0.62; 1.99	0.72	1.22	0.62; 2.42	0.57
Age at RP	-1.4	-2.1; -0.8	<0.001	1.14	1.09; 1.19	<0.001	0.92	0.87; 0.97	0.002
Risk Group									
Low	Ref			Ref			Ref		
Intermed.	-9.8	-22.6; 3.0	0.13	1.38	0.60; 3.17	0.45	0.70	0.24; 2.04	0.51
High	-15.7	-31.2; -0.2	0.047	2.10	0.76; 5.77	0.15	0.36	0.10; 1.25	0.11
Co-morbidity									
No	Ref			Ref			Ref		
Yes	-7.4	-19.5; 4.8	0.23	1.78	0.82; 3.87	0.14	0.67	0.28; 1.57	0.35
Marital status									
Paired	Ref			Ref.			Ref		
Single	-3.5	-16.1; 9.0	0.58	0.83	0.37; 1.88	0.66	1.27	0.47; 3.52	0.64
Education									
High	Ref			Ref			Ref		
Intermed/low	-5.2	-13.4; 2.9	0.21	1.41	0.83; 2.37	0.20	0.90	0.47; 1.72	0.75
Type D personality									
No	Ref			Ref			Ref		
Yes	-5.6	-19.2; 8.0	0.42	1.65	0.68; 4.05	0.27	0.69	0.25; 1.94	0.49
Pre-Treatm SexSS /Erect.Dysf.	0.53	0.35 ; 0.71	<0.001	7.16	2.38; 21.5	<0.001	NA³	NA	NA

¹Sexual Summary Score; ²95% confidence interval; ³Not available