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Seminal vesical sparing cystectomy in bladder cancer patients is feasible with good functional results without impairing oncological outcomes: A longitudinal long-term propensity-matched single center study.

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Abstract

Purpose: Seminal-vesicle-sparing radical-cystectomy has been reported to improve short-term functional-results without compromising oncological outcomes. However, there is still a lack of data on long-term outcomes after seminal-vesicle-sparing radical-cystectomy. The aim of this study was to compare oncological and functional outcomes in patients after seminal-vesicle-sparing vs non- seminal-vesicle-sparing radical-cystectomy.

Material and Methods: Oncological and functional outcomes of 470 consecutive patients after radical-cystectomy and orthotopic ileal reservoir from 2000 to 2017 were evaluated. They were stratified into 6 groups according to nerve-sparing and seminal-vesicle-sparing

status as attempted during surgery: no-sparing at all (n=55), unilateral-nerve-sparing (n=159), bilateral-nerve-sparing (n=132), unilateral-seminal-vesicle-sparing and unilateral- nerve-sparing (n=30), unilateral-seminal-vesicle-sparing and bilateral-nerve-sparing (n=45), and bilateral seminal-vesicle-sparing (n=49) and used propensity modelling to adjust for preoperative differences.

Results: Median follow-up among the entire cohort was 64months. Among the 6 groups, our analysis showed no difference in local recurrence-free survival (p=0.173). However, progression free, cancer-specific and overall survival were more favourable in patients with seminal-vesicle-sparing radical-cystectomy (p<0.001, p=0.006 and p<0.001, respectively). Proportions of patients with erectile function recovery were higher in the seminal-vesicle-sparing groups at all time points in all analyses, respectively, with pronounced earlier recovery in patients with bilateral-SVS. Importantly, patients with seminal-vesicle-sparing were significantly less in need of erectile aids to achieve erection and intercourse. Over the whole period, daytime urinary-continence was significantly better in the seminal-vesicle-sparing groups (OR 2.64 to 5.21).

Conclusions: In a highly selected group of patients, seminal-vesicle-sparing radical-cystectomy is oncologically safe and results in excellent functional outcomes that are reached at an earlier timepoint after surgery and remain superior over a longer period of time.

1. Introduction

After RC, depending on the pT, 40-80% of patients are long-term-survivors, among these some with pelvic-node-involvement. Consequently, postoperative morbidity of RC, such as UI after OBS and ED which have a major-effect on QoL, should be kept as low as possible[1, 2]. Several attempts at SPC have been reported to improve UI and ED after RC and OBS [2-11]. These approaches aim to minimize damage to the pelvic-plexus, NVBs, and the external urinary-sphincter during surgery [12]. Because of the high prevalence of occult-malignancy in the prostate and the possibility of UCa in prostatic-ducts[13], we never advocated prostate-sparing-RC, but in well-selected cases we practiced uni-or bilateral-SVS-RC in order to minimize possible damage to the pelvic-plexus adjacent to the SV and in the vesicoprostatic-angle[12].

A systematic-review by Hernández et al[14] reported recently that prostate-, capsule-, seminal-vesicle, and nerve-sparing-cystectomy is associated with more favorable functional-outcomes compared with standard-RC without compromising oncological-outcomes. For analysis of both functional and oncological-outcomes, the studies only included patients with short-to mid-term follow-up, and the quality of the evidence was low-to-moderate. Hence, numerous uncertainties remain[14].

Aim of this study was to analyse long-term-UC and EFR of patients after RC combined with SVS-surgery and compare it to a propensity-score-weighted group of patients without SVS-RC.

2. Materials and Methods

In this long-term-single-centre cohort-study, we reviewed data of 486 consecutive male patients who underwent RC and OBS at our institution from 2000 to 2017. Ethics-approval has been obtained (KEK-Be 2016-00660).

2.1. Patient selection

To achieve the best possible local tumour-control, patients with BC considered for SVS-RC were selected restrictively[2]. A rigid-urethrocystoscopy with paracollicular-biopsies and bimanual-palpation was performed in all patients before the decision for SVS was made. For inclusion-and exclusion-criteria for SVS-RC see Table1a. The anatomo-pathological basis for these exclusion-criteria is that BC located at or distal to the trigone represents a high-risk factor for prostatic-UCa which requires adherence to principles of oncosurgical-radicality in order not to compromise oncological-outcomes. Similarly, in case of ipisilateral dorsal, lateral or posterior bladder-wall maximum margin to the tumour should be achieved. Hence, the SV should be removed in those cases. Patients with non-organ-confined tumour were not considered to be eligible for SVS[8, 15].

2.2. Staging, follow-up data collection

All patients had preoperative staging and were followed prospectively according to the institutional follow-up-protocol published earlier[16-21]; In this process, the early and ongoing involvement of urologists as well as providing different sources of information to patients as well as to apprehend patient-reported outcomes is crucial[22, 23].

2.3. Surgical procedure

The surgical-technique for NS-RC, PLND and OBS has been described previously[2, 3, 24].

In brief, first, the NVB were cleaved away from the prostatic-capsule and detached. Second, the SV(s) were identified after a sharp transverse incision of the peritoneum was made over the vas deferens and SV. A plane of dissection was developed bluntly between the SV(s) and the dorsal bladder-wall. The dorsomedial bladder-pedicle was transsected close to the bladder-wall at the level of the SVs, thus away from the pelvic-plexus, which is located lateral and dorsal to the SV. Dissection then proceeded caudally very close to the vesicoprostatic angle to avoid damage to the paraprostatic-NVB. Next a lateral incision of the prostatic-capsule ventral to the NVB was made running from base-to-apex. Then, the urethra was transected sharply at the level of the distal verumontanum. Frozen-sections were not routinely taken during the en-bloc-resection.

2.4. Functional outcomes

Assessment of functional-results were described in detail previously[3, 16, 25]. In brief, UC and EFR were assessed preoperatively and at each follow-up-visit using previously published standardized-questionnaires[17] and since 2004 with the ICIQ-UI-SF and IIEF-15-questionnaires[26-28].

Patients were classified as continent if they required ≤1 pad for safety reasons during the day or at night. Intact erectile-function preoperatively and EFR was defined as the ability to achieve an erection sufficient for penetration and maintenance of intercourse with or without medical-aids[16].

2.5. Statistical analyses

We conducted five separate propensity analyses, 1) no-SVS versus SVS, 2) bilateral-SVS versus bilateral-NS, 3) unilateral-SVS versus unilateral-NS, 4) no-NS versus any-SVS and 5)

no-SVS versus SVS including only patients with erectile-function at time of surgery. Analyses 1) to 3) cover the surgical options, 4) and 5) are sensitivity-analysis. In each analysis, we used IPTW to construct balanced treatment groups with respect to risk of function loss and baseline-characteristics (see Supplemental-material).

Patients with benign conditions have not been included in the analysis of oncological-outcomes. Additionally, we excluded patients with benign conditions (n=10) as a further sensitivity analysis in order to derive the impact of SVS on bladder cancer patients only.

We investigated the treatment-impact on oncological-endpoints calculating HR with 95%CI after IPTW. KM-curves for all six treatment groups were plotted crudely (before IPTW) with p-values from log-rank-tests. Statistical analyses were performed using Stata16 (StataCorp, College Station, Texas, USA). For further details of the statistical methods see supplemental material (Supplemental-material).

3. Results

Mean age at surgery of the entire cohort was 63.7 (SD 8.9) years, and median follow-up was 5.3 (IQR 1.9-10.0) years (Table 1b). Of the 486 patients, 16(3%) were excluded from analyses due to previous or early postoperative radiotherapy within 90days and 470 were included.

3.1. Propensity score matching

Propensity scores showed good overlap in all treatment-group comparisons before and after IPTW (Figure1a-c), standardized differences of pre-operative variables were below 0.1, except tumour stage and lymph node metastasis in the comparison of bilateral-NS versus bilateral-SVS, which was 0.165 and 0.115, respectively, indicating no meaningful differences between treatment-groups (Figure1d-e and Suppl.Table1a-c). As shown in

Suppl.Table1d, standardized-differences between patients without any-NS or SVS and patients with SVS (sensitivity-analysis 1) remained large also after IPTW, so results might still be confounded, whereas standardized-differences between patients with and without SVS with intact erectile-function preoperatively (sensitivity-analysis 2) all dropped ≤0.06, see Suppl.Table1e.

3.2. Oncological outcomes

3.2.1. PSM and local recurrence

A PSM was seen in six patients of the study-cohort (1.3%). There was no significant difference in PSM of BC among the six groups (p=0.71). Furthermore, our un-adjusted analysis showed no difference in local-recurrence-free survival among the 6 groups (p=0.173).

Urethral-recurrence occurred in 5% (24/470) patients after a median-time of 1year (IQR 0.6-2). Four patients (1%) had a local-recurrence other than urethral (median 0.5 years, IQR 0.4-1.7).

3.2.2. Upper tract recurrence and distant metastasis

Upper tract recurrence was observed in 4%(18/470) patients, after a median-time of 2.1years(1.0-7.4). Twenty-six percent of patients(122/470) had distant metastasis after a median time of 0.95(0.5 -2) years.

3.2.3. Kaplan-Meier curves

Figure2 shows follow-up with respect to all oncological outcomes as crude Kaplan-Meier curves up to 10years after surgery. PFS, CSS and OS and were more favorable in patients with SVS-RC ($p<0.001$, $p=0.006$ and $p<0.001$, respectively). Highest mortality was seen in patients without SVS or NS-RC (Table2a-b). HR after IPTW were below one for all outcomes in SVS vs no-SVS except CSS, indicating a reduced risk of the outcome after SVS. Uni- and bilateral comparisons did not show any association, except for PFS after unilateral SVS (Table2c). Incidental prostate-cancer was found in 34% with SVS and in 43% without SVS. PSM-rate of the prostate-cancer was 7% and 5% with and without SVS, respectively. Incidental prostate-cancer at RC was not associated with inferior OS, HR (95%CI), 1.18 (0.87-1.59).

3.3. Functional outcomes

3.3.1. Erectile function recovery

Our primary functional-outcome was EFR in the time period from 3months to five years after surgery. After IPTW, proportions of patients with EFR were higher in the SVS-groups at all time points in all analyses, respectively, with pronounced earlier recovery in patients with bilateral-SVS (Figure 3A-C, SupplementalTable 2). Accumulated for the whole period this corresponds to a higher proportion of patients with EFR, OR 12.3 (95%CI 5.74 to 26.2, $p<0.001$) for SVS versus no-SVS, 16.8 (3.28 to 85.6, $p=0.001$) for bilateral-SVS vs bilateral-NS and 8.60 (3.68 to 20.1, $p<0.001$) for unilateral-SVS vs unilateral-NS. Importantly, patients with SVS were significantly less in need of erectile-aid (PDE-5-inhibitors, Alprostadil by use of MUSE or autoinjection therapy) to achieve erection and intercourse, respectively (Table3a).

Erections sufficient for intercourse were more frequent in the SVS-groups (see SupplementalTable 3 for every time point) with an overall-OR of 6.75 to 9.78 indicating that less invasive support was needed to achieve the ability of intercourse after SVS-vs no-SVS.

Tables 3b) and 3c) show the results of our sensitivity-analyses. When comparison was restricted to no-NS versus any-SVS, treatment effects became very large, but may be influenced by residual confounding due to imbalance among treatment-groups. The analysis which focused on patients with erectile-function at time of surgery yielded a functional benefit of SVS in every respect. The odds of EFR is 10times higher after SVS in this patient-group.

3.3.2. Urinary continence

Daytime-UC was in general high from 6months postoperatively onwards with slightly higher proportions in patients after SVS at every single time-point, except for bilateral-NS vs bilateral-SVS, where proportions were basically the same from one year on. Over the whole period, daytime-UC was significantly better in the SVS-groups (OR 2.64 to 5.21). With respect to nighttime-UC, found higher proportions after SVS in all comparisons, which did not reach statistical-significance for unilateral-NS vs unilateral-SVS (Figure 4A-C, and SupplementalTable 4).

3.3.3. Residual urine

SVS decreased the proportion of patients with residual-urine ≥50ml, yielding ORs markedly below one, however not reaching statistical significance for bilateral-SVS vs bilateral-NS (Figure3d-e and Table3).

3.3.4. Sensitivity analysis for bladder cancer patients only

After excluding patients with benign disease, propensity modelling worked equally well, and the OR of SVS showed similar patterns for functional outcomes, except that nighttime continence did not reach statistical significance, see Supplemental Table 5, and Supplemental Figures 1 and 2.

4. Discussion

Our analysis yielded several important findings. Most importantly, oncological-outcomes were not inferior in all degrees of SVS. Second, we found an earlier recovery of UC in patients with SVS compared to NS only. Likewise, SVS has a beneficial impact on early-EFR which remains significantly better over a longer period of time. Having conducted a propensity-score-weighting, the estimation of the effect of SVS on functional and-oncological outcomes is even more valid.

Our rate of local recurrence other than urethral of 6% in patients after SVS-RC is in line with the data of Hernandez et al which reported rates after SPC between 2.2-16.1%[14]. In patients with SVS-RC reported 5-or 6y-CSS-and OS-rates range from 35-93% and 47-93%, respectively.[4-6, 8, 11]. Our 5-and 10y-CSS and OS in patients with SVS was similar with 87% and 81%,and 80% and 71%, respectively.

In our series, local recurrence-free-survival was similar among all groups, PFS, CSS and OS were more favorable for the SVS-group. This is, propensity-weighting notwithstanding, clearly owing to a very careful patient-selection with a remaining bias. Patients have to fulfill certain inclusion-criteria to be considered for SVS. Therefore, a general applicability of these findings to all patients undergoing RC for BC is not possible. Hence, we believe that this

technique, a careful patient selection provided, constitutes no compromise of oncological-principles, even in the case of unexpected limited invasion of the UCa into the prostate.

Hernandez et al reported day-and nighttime-continence from 88.9-100% and 55-88.9%, respectively[14]. However, with the exception of two comparative-studies of Basiri et al and Mertens et al[5, 29] no difference in favor of the sexual-preserving-technique was observed in other studies. However, we could show that UC-recovery was significantly better in the SVS-groups during daytime (OR 2.64 to 5.21) and, less pronounced, during nighttime (OR 1.08 to 4.37) in any of our comparisons. This might be because the hypogastric nerve fibres which run along the tip of the SV can be spared more extensively with the SVS-approach as compared to the NS-approach[3, 30]. Therefore, in order to optimize urinary-continence, we are always aiming at sparing the SV if it's safe from an oncological standpoint. Hence, this is the reason why we perform SVS in some patients even with decreased erectile function preoperatively. Hence, although baseline sexual function clearly plays an important role in the decision whether SVS should be aimed at, it is not the only variable we take into account.

From a neuroanatomical point of view, the earlier recovery in daytime-continence may be explained with lesser extent of neurapraxia which normally resolves within 24months postoperatively. The better UC-rates over time though is likely due to less harm to the nerves surrounding the tips of the SVs[12]. This is substantiated by the studies by Roethlisberger et al who could demonstrate in their anatomical study on embalmed hemipelves that the innervation of the urethra and the corpora cavernosa derives from two origins. Not only from the inferior part of the pelvic-plexus which runs towards the apex of the prostate and the rhabdosphincter, but also a more superior-part from a sub-plexus around the SVs which innervates the more proximal prostate and the prostatic-urethra with the lissosphincter.

Furthermore, a connection between the two parts was demonstrated in approximately one third of the samples investigated. This could explain the significantly better recovery of continence after pelvic surgery[30].

In line with our data, reported EFR in the systematic review of Hernandez et al were significantly better compared to standard-cystectomy, ranging from 58-94% for SPC[14]. Our present study is the first which compares the different SVS-grades, but also different SVS-grades to NS-RC and standard-RC. Many studies included were heterogenous (i.e.studies included laparaoscopic and robotic-surgery and heterotopic urinary diversion) and did not compare different sexual-sparing-techniques to standard-cystectomy at all. In our cohort, after IPTW, this comparison showed likewise significantly better functional-outcomes in favor of patients with SVS (see SupplementalTables2-4). We also tried to construct comparable groups of patients without any NS or SVS and patients with SVS using propensity-modelling, but baseline-characteristics between the two subcohorts differed substantially even after IPTW (standardized-differences >0.1). Therefore, results of comparison of these treatment-groups have to be interpreted with caution, as residual-confounding is likely. Importantly, all patients with SVS underwent also NS as technically, the SV cannot be spared without sparing the nerves. Hence, for reasons of surgical feasibility, the true effect of SVS is entangled with the effect of NS.

Furthermore, follow-up for EFR and UC was only 6 to 12months in most of the studies, whereas our median follow-up was 64months. This is of paramount importance to assess the impact of SPC, as we could demonstrate that patients suffering from UI and ED may regain function even after 12months whereby the beneficial impact of SPC on UI and ED becomes even more apparent over time. This may be due to the ongoing resolution of neurapraxia seen up to 2years after major pelvic surgery [3, 16].

The main limitation of the present study is lack of randomisation of BC-patients undergoing SVS vs non-SVS resulting in a certain selection-bias with poorer survival-data in the non-SVS-group, owing to more advanced-disease. However, we overcame this limitation at least partially with propensity score-weighted-analysis. Furthermore, those encouraging survival-data attest the careful selection of patients undergoing SVS-RC which is of utmost importance to achieve good oncological and functional-outcomes. Whether a preoperative-MRI might optimize patient-selection is under current investigation.

5. Conclusion

In a highly-selected group of patients, SVS-RC is oncologically safe and results in excellent functional-outcomes that are achieved at an earlier timepoint postoperatively and remain superior over a longer time-period.

Abbreviations and Acronyms

RC = radical cystoprostatectomy

pT = pathological tumour stage

UI = urinary incontinence

OBS = orthotopic bladder substitution

ED = erectile dysfunction

QoL = quality of life

SPC = sexual-preserving cystectomy

UCa = urothelial cancer

NVB = neurovascular bundle

SV(s) = seminal vesicle(s)

SVS-RC = seminal vesicle-sparing cystectomy

EFR = erectile function recovery

UC = urinary continence

BC = bladder cancer

CT = computed tomography

MRI = magnetic resonance imaging

NS = nerve sparing

PLND = pelvic lymph node dissection

ICIQ-UI-SF = International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form

IIEF = International Index of Erectile Function

IPTW = inverse probability of treatment weighing

HR = hazard ratio

CI = confidence interval

IQR = interquartile range

PSM = positive surgical margin

PFS = progression free-survival

CSS = cancer-specific survival

OS = overall survival

HR = hazard ratio

OR = odds ratio

PDE-5 = Phosphodiesterase-5

MUSE = Medicated Urethral System for Erection

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Table 1a: Inclusion and exclusion criteria for seminal vesicle sparing radical cystectomy

Exclusion criteria for any SVS	Inclusion criteria for unilateral SVS	Inclusion criteria for bilateral SVS
Location of tumour at trigonal area and bladder neck	Tumour only in contralateral dorsal, lateral or posterior bladder wall	Bladder dome and anterior bladder wall tumours only
Invasive tumour in prostatic urethra (paracollicular area)		Benign conditions (e.g. low-compliance bladder or shrunken bladder)
Clinically non-organ-confined tumour		

SVS, seminal vesicle sparing

Table 1b: Baseline characteristics of 470 patients with bladder cancer undergoing radical cystectomy

	no NS/SVS	Uni-NS, no SVS	Bi-NS, no SVS	Uni-NS, Uni-SVS	Bi-NS, Uni-SVS	Bi-SVS	*P*-value
Number of patients	**55**	**159**	**132**	**30**	**45**	**49**	
Preoperative							
Age [years], mean (SD)	65 (9.2)	64 (8.7)	64 (7.6)	62 (8.8)	62 (8.8)	61 (12)	0.21
BMI [kg/m2], mean (SD)	27 (4.1)	27 (5.1)	27 (3.9)	26 (3.3)	27 (4.4)	27 (4.5)	0.81
CACI ≥ 3, n (%)	5 (9.1)	36 (23)	28 (21)	5 (17)	4 (8.9)	14 (29)	0.045
Hypertension, n (%)	28 (51)	77 (48)	57 (43)	17 (57)	17 (38)	23 (47)	0.57
Coronary artery disease, n (%)	13 (24)	37 (23)	24 (18)	7 (23)	6 (13)	11 (22)	0.67
Hypercholesterinemia, n (%)	9 (16)	36 (23)	28 (21)	11 (37)	7 (16)	18 (37)	0.05
Diabetes, n (%)	13 (24)	15 (9.4)	14 (11)	4 (13)	4 (8.9)	5 (10)	0.16
COPD, n (%)	6 (11)	31 (19)	22 (17)	8 (27)	8 (18)	9 (18)	0.56
Nicotine, n (%)	35 (64)	106 (67)	88 (67)	21 (70)	21 (47)	29 (59)	0.19
Multiple TUR-B, n (%)	17 (31)	35 (22)	42 (32)	5 (17)	10 (22)	20 (41)	0.06
Pathological tumor stage [TUR-B], n (%)							<0.001
≤pTa	1 (1.8)	2 (1.3)	12 (9.1)	0 (0)	1 (2.2)	11 (22)	
pT1	16 (29)	24 (15)	34 (26)	7 (23)	11 (24)	17 (35)	
pT2	38 (69)	133 (84)	86 (65)	23 (77)	33 (73)	21 (43)	
Carcinoma in situ [TUR-B], n (%)	16 (29)	45 (28)	48 (36)	7 (23)	13 (29)	16 (33)	0.66
Histological variants [TUR-B], n (%)							0.87
squamous differentiation	1 (1.8)	5 (3.1)	1 (0.76)	1 (3.3)	3 (6.7)	1 (2.0)	
small cell/neuroendocrine different.	0 (0)	3 (1.9)	1 (0.76)	0 (0)	2 (4.4)	0 (0)	
sarcomatoide differentiation	0 (0)	3 (1.9)	3 (2.3)	0 (0)	2 (4.4)	1 (2.0)	
other variants	0 (0)	2 (1.3)	3 (2.3)	0 (0)	0 (0)	0 (0)	
Lymphovascular invasion, n (%)	3 (5.5)	23 (14)	13 (10)	3 (10)	7 (16)	5 (10)	0.48
Hydronephrosis, n (%)	10 (18)	35 (22)	24 (18)	3 (10)	3 (6.7)	9 (18)	0.21
Intravesical instillation, n (%)	13 (24)	27 (17)	35 (27)	1 (3.3)	12 (27)	21 (43)	<0.001
Neoadjuvant chemotherapy, n (%)	5 (9.1)	34 (21)	21 (16)	2 (6.7)	9 (20)	4 (8.2)	0.08
Adjuvant/palliative chemotherapy, n (%)	21 (38)	50 (31)	31 (23)	8 (27)	6 (13)	7 (14)	0.013
Paracollicular biopsy, n (%)							0.73
negative	50 (91)	153 (96)	121 (92)	30 (100)	44 (98)	48 (98)	
CIS	3 (5.5)	3 (1.9)	7 (5.3)	0 (0)	1 (2.2)	0 (0)	
pTa G1-2	1 (1.8)	0 (0)	1 (0.76)	0 (0)	0 (0)	0 (0)	
pTa G3	0 (0)	2 (1.3)	1 (0.76)	0 (0)	0 (0)	0 (0)	
≥ T1	1 (1.8)	1 (0.63)	2 (1.5)	0 (0)	0 (0)	1 (2.0)	
Intact erectile function at baseline, n (%)	34 (89)	106 (79)	94 (81)	23 (79)	34 (79)	36 (80)	0.79
Postoperative							
Tumor pathology, n (%)							<0.001
pT0	0 (0)	9 (5.7)	22 (17)	1 (3.3)	9 (20)	10 (20)	
pT1	14 (25)	24 (15)	39 (30)	8 (27)	12 (27)	19 (39)	
pT2	17 (31)	59 (37)	44 (33)	15 (50)	14 (31)	9 (18)	
pT3	16 (29)	59 (37)	25 (19)	5 (17)	10 (22)	10 (20)	
pT4	8 (15)	8 (5.0)	2 (1.5)	1 (3.3)	0 (0.0)	1 (2.0)	
Lymph node metastasis [pN+], n (%)	19 (35)	48 (30)	18 (14)	9 (30)	4 (8.9)	3 (6.1)	<0.001
Number of lymph nodes removed	29 (9.1)	34 (14)	38 (17)	37 (23)	39 (13)	29 (16)	<0.001
CIS pathology, n (%)	22 (40)	67 (42)	61 (46)	10 (33)	27 (60)	23 (47)	0.23
High grade [G3], n (%)	55 (100)	148 (93)	108 (82)	25 (83)	39 (87)	36 (73)	<0.001
PSM bladder cancer, n (%)	1 (1.8)	1 (0.63)	2 (1.5)	0 (0)	1 (2.2)	1 (2.0)	0.71
incidental prostate cancer, n (%)	20 (36)	69 (43)	59 (45)	14 (47)	16 (36)	15 (31)	0.69
PSM prostate cancer, n (%)	2 (10)	4 (6)	1 (2)	2 (14)	1 (6)	0 (0)	0.33

NS, nerve sparing; SVS, seminal vesicle sparing; BMI, body mass index; CACI, Charlson-Age Comorbidity Index; COPD, chronic obstructive pulmonary disease; TUR-B, transurethral resection of the bladder; CIS, carcinoma in situ; PSM, positive surgical margin

Percentages may not sum to 100% due to rounding

Table 2: Occurrence of recurrence and survival data of 470 patients undergoing radical cystectomy and orthotopic bladder substitution

Table 2a: Number of local and distant recurrences and time to recurrence

Localization	n (%)	median (IQR)
Urethral recurrence	24 (5)	1.0 (0.6 – 2.0)
Recurrence upper urinary tract	18 (4)	2.1 (1.0 – 7.4)
Local recurrence other than urethral*	28 (6)	1.1 (0.5 – 2.1)
Distant metastasis*	122 (26)	1.0 (0.5 – 2.0)

**Local recurrence was defined as recurrence in the pelvic soft tissue or pelvic lymph nodes detected with imaging studies. Involvement of lymph nodes above the level of the iliac bifurcation and visceral metastasis was classified as distant metastasis.*

	1 year			2 years			5 years			10 years		
	all	*no SVS*	*SVS*	*all*	*no SVS*	*SVS*	*all*	*no SVS*	*SVS*	*all*	*no SVS*	*SVS*
Local recurrence-free survival (%)	98	97	100	97	95	100	96	93	99	95	92	99
Progression-free survival (%)	81	79	83	75	70	82	67	59	75	57	51	65
Cancer-specific survival (%)	95	93	96	87	86	89	79	75	84	74	69	79
Overall survival (%)	92	89	95	84	80	88	72	67	78	62	56	69

Table 2b: Survival data after inverse probability of treatment weighing

Table 2c: Safety analysis: impact of SVS on tumor recurrence and death - inverse probability of treatment-weighted hazard ratios of SVS on time-to-event oncological outcomes

	No SVS vs SVS		Bilateral NS vs bilateral SVS		Unilateral NS vs unilateral SVS	
	HR (95% CI)	*p*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*
Local recurrence-free survival	0.16 (0.04 to 0.66)	0.012	0.18 (0.02 to 1.42)	0.105	0.19 (0.02 to 1.60)	0.128
Progression-free survival	0.59 (0.38 to 0.91)	0.018	0.94 (0.47 to 1.88)	0.860	0.53 (0.29 to 0.99)	0.047
Cancer-specific survival	0.65 (0.36 to 1.19)	0.165	1.02 (0.37 to 2.83)	0.966	0.59 (0.26 to 1.35)	0.214
Overall survival	0.59 (0.36 to 0.96)	0.035	1.12 (0.54 to 2.33)	0.769	0.49 (0.23 to 1.01)	0.054

SVS, seminal vesicle sparing; NS, nerve sparing; HR, hazard ratio; CI, confidence interval

Table 3: Erectile function and urinary continence 3 months to 5 years after surgery of SVS as compared to no SVS

Table 3a: IPT-weighted odds ratio of preserved erectile function 3 months to 5 years after surgery of SVS as compared to no SVS

	No SVS vs SVS		Bilateral NS vs bilateral SVS		Unilateral NS vs unilateral SVS	
	OR (95% CI)	***P value***	***OR (95% CI)***	***P value***	***OR (95% CI)***	***P value***
EFR	12.3 (5.74 to 26.2)	<0.001	16.8 (3.28 to 85.6)	0.001	8.60 (3.68 to 20.1)	<0.001
*Erection**	1.75 (1.17 to 2.64)	0.007	1.21 (0.63 to 2.31)	0.564	1.98 (1.14 to 3.46)	0.016
*Aid**(ordinal)*	9.27 (4.64 to 18.5)	<0.001	9.78 (2.73 to 35.1)	<0.001	6.75 (2.98 to 15.3)	<0.001
Daytime continence	4.65 (2.75 to 7.88)	<0.001	2.64 (1.14 to 6.12)	0.023	5.21 (2.45 to 11.1)	<0.001
Nighttime continence	1.94 (1.07 to 3.52)	0.028	4.37 (1.67 to 11.4)	0.003	1.08 (0.48 to 2.41)	0.852
Residual urine ≥ 50ml	0.29 (0.15 to 0.56)	<0.001	0.57 (0.23 to 1.42)	0.225	0.25 (0.09 to 0.66)	0.005

Table 3b: Sensitivity analysis 1

IPT-weighted odds ratio of preserved organ function 3 months to 5 years after SVS surgery (n=124) as compared to no SVS (n=55) in patients with standard radical cystectomy vs. any SVS.

	SVS vs no SVS	
	OR (95% CI)	***P value***
EFR	155 (32.96 to 733)	<0.001
*Erection**	2.81 (1.07 to 7.36)	0.036
*Aid**(ordinal)*	78.7 (24.8 to 250)	<0.001
Daytime continence	5.19 (2.04 to 13.2)	0.001
Nighttime continence	6.20 (2.09 to 18.4)	0.001
Residual urine ≥ 50ml	0.18 (0.08 to 0.43)	<0.001

Table 3c: Sensitivity analysis 2

IPT-weighted odds ratio of preserved organ function 3 months to 5 years after surgery of SVS (n=108) as compared to no SVS (n=257) in patients with preserved erectile function pre-operatively.

	SVS vs no SVS	
	OR (95% CI)	***P value***
EFR	10.5 (4.97 to 22.3)	<0.001
*Erection**	1.68 (1.11 to 2.54)	0.014
*Aid**(ordinal)*	8.51 (4.17 to 17.4)	<0.001
Daytime continence	2.73 (1.56 to 4.77)	<0.001
Nighttime continence	1.66 (0.90 to 3.08)	0.106
Residual urine ≥ 50ml	0.30 (0.14 to 0.67)	0.003

SVS, seminal vesicle sparing; EFR, erectile function recovery; UC, urinary continence; OR, odds ratio; CI, confidence interval.

**Iterations did not converge, so the estimate is based on a generalized estimating equation-model.*

***"Aid" denotes the amount of support needed for sexual intercourse, the OR expresses how likely it is that a patient after SVS need less support as compared to a patient after no-SVS.*

Remark: p values related to continence during day were relatively low because proportions of continent patients were close to 100% for most time points, so confidence intervals of the proportions are small. Hence, differences between treatment groups appeared more significant as compared to continence during night for each time point *(see Figure 4 and Supplemental table 4)* and especially for the entire period, as low variability leads to higher precision.

Figure 1: Propensity models

Figure 1a-c: *Standardized differences before and after IPTW in three different propensity models*

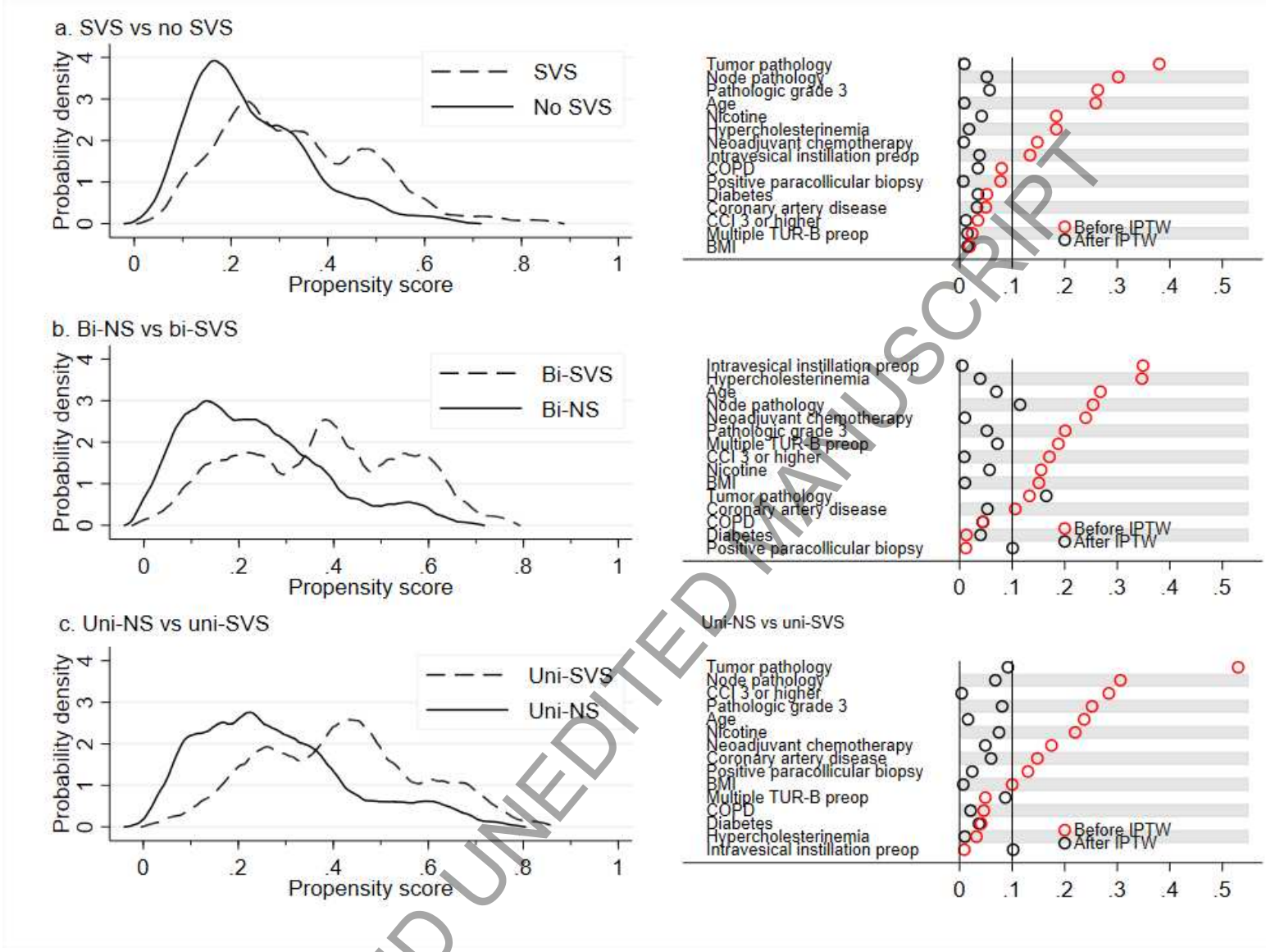

Figure 1d-e: *Standardized differences before and after IPTW, sensitivity analyses*

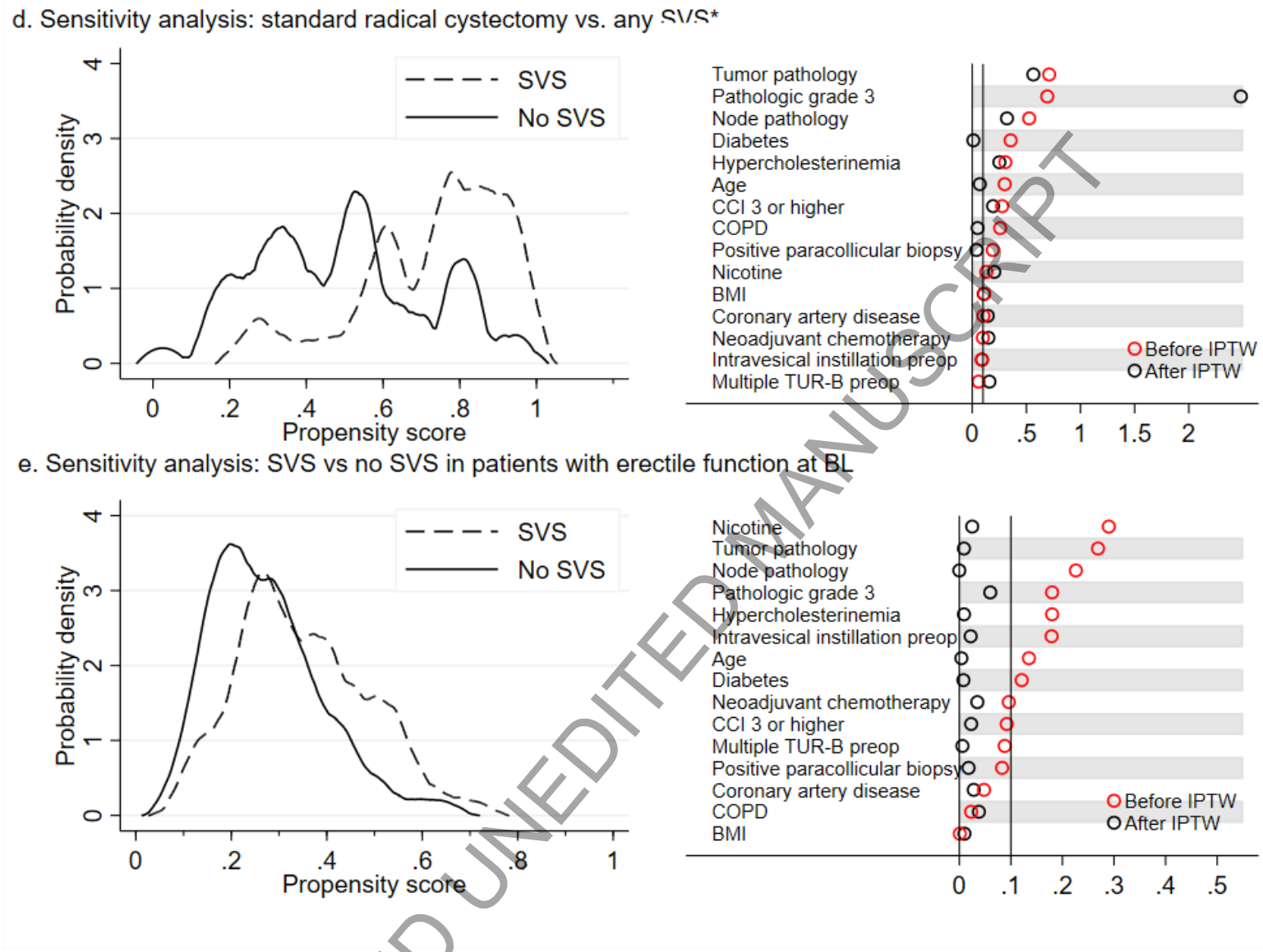

Figure 2: Kaplan-Meier curves of oncological endpoints after IPTW

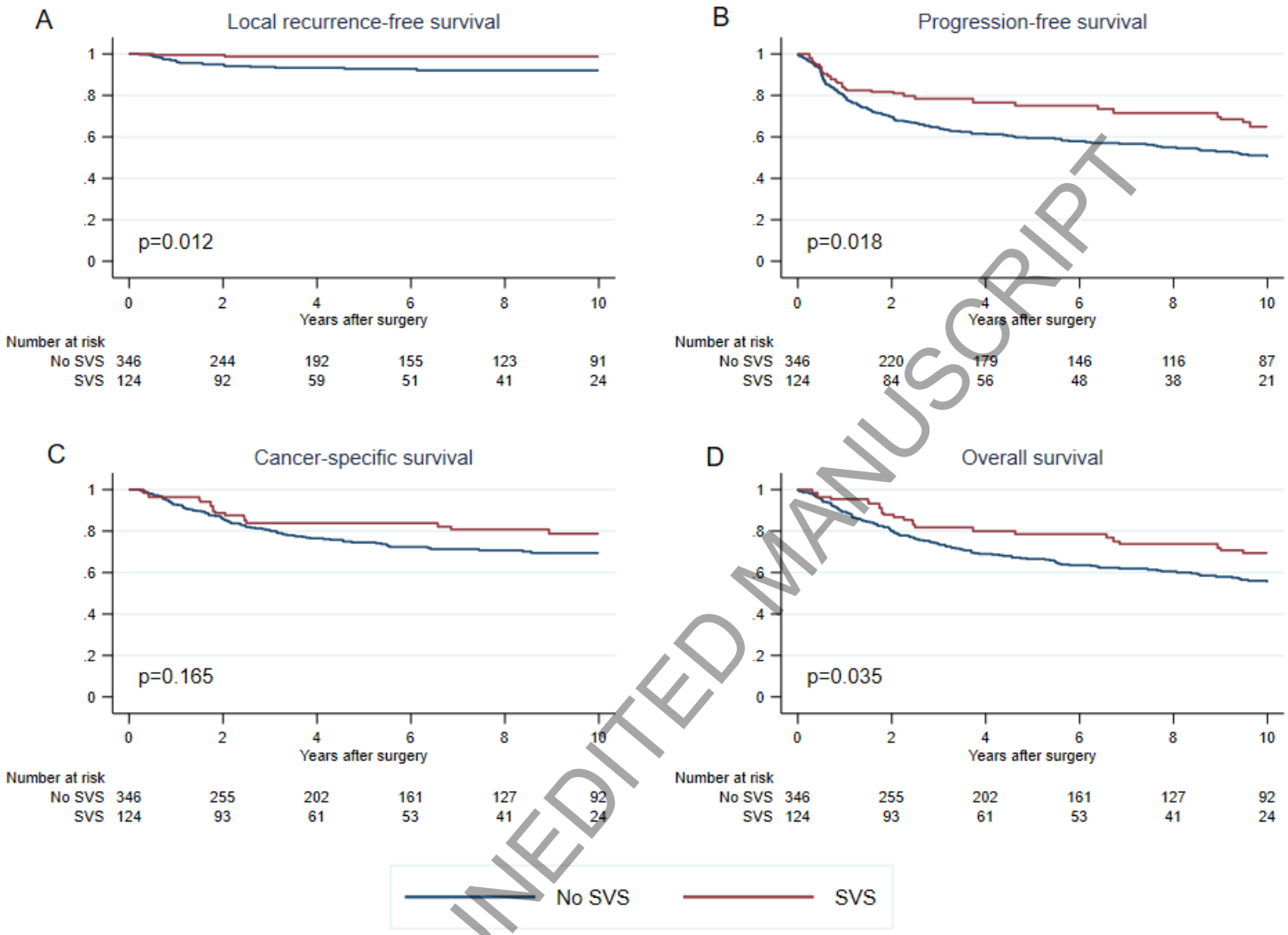

Figure 3: postoperative rates of erectile function recovery and erection not sufficient for intercourse

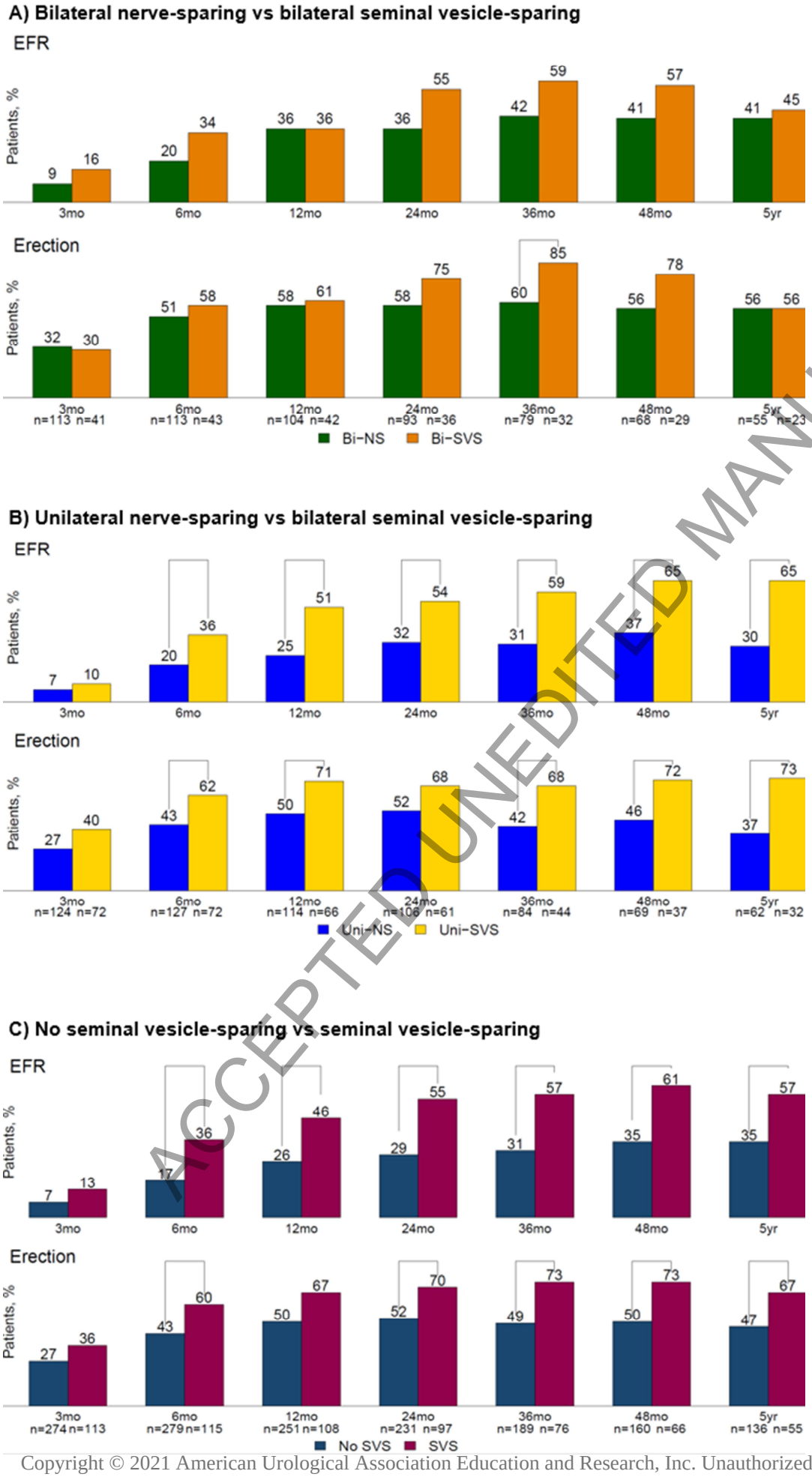

Figure 4: postoperative rates of day and nighttime continence, and residual urine