A Prospective Analysis of the Effects of Nerve-Sparing Radical Prostatectomy on Urinary Continence Based on Expanded Prostate Cancer Index Composite and International Index of Erectile Function Scoring Systems

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Purpose: This study aims to objectively characterize the effect of successful nerve sparing (NS) during radical prostatectomy (RP) on postoperative urinary continence (UC) using International Index of Erectile Function (IIEF)-scores and a previously described Expanded Prostate Cancer Index Composite (EPIC) score cutoff value (COV) for UC. Several notable studies on this topic present conflicting outcomes. This is largely due to a lack of clear definitions and consensus regarding preserved erectile function (EF) and UC.

Methods: This study is comprised of all patients who underwent RP at the Kantonsspital Baden, Switzerland, between 2004 and 2013. Patients completed self-assessment questionnaires for UC (EPIC) and EF (IIEF) pre- and postoperatively (3, 6, 9, 12, 18, and 24 months; yearly thereafter). We used a previously described EPIC subscore COV, with "satisfactory continence" signified by a score > 85. Statistical analysis was performed using Kaplan-Meier and Cox regression analyses for "surgeon-" and "IIEF-defined" NS definitions.

Results: Of 236 men with a median age of 63 years (interquartile range [IQR], 59–66 years) and median follow-up time of 48 months (IQR, 30–78 months), 176 underwent unilateral (n = 33) or bilateral (n = 143) NS RP. Fifty-four underwent non-NS (NNS) RP. Kaplan-Meier analyses identified the following risk factors for UC: age, prostate volume, cancer risk group, and NS status. In surgeon-defined NS RP cases, multivariate analysis for regaining continence demonstrated no significant difference (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.48–1.25; P = 0.3). With successful IIEF-defined NS RPs, regression analysis demonstrated no significant difference (HR, 0.89; 95% CI, 0.59–1.35; P = 0.58).

Conclusions: In our population, analysis and comparison of surgeon- and IIEF-defined NS and NNS cohorts revealed that NS RP did not improve postoperative UC. The conservation of UC alone should not motivate surgeons or patients to pursue NS RP.

Keywords: Prostate; Prostatectomy; Urinary incontinence; Self-assessment
INTRODUCTION

While achieving the “trifecta” — being cancer-free, continent and potent — is the commonly anticipated goal of many radical prostatectomy (RP) patients, issues such as urinary incontinence (UI) and erectile dysfunction (ED) are often realities that considerably impact their quality of life (QoL) [1]. The nerve-sparing (NS) RP, pioneered by Walsh et al. [1] in the 1980s, sought to reduce rates of UI and ED through careful dissection of the neurovascular bundles away from the prostate during prostatectomy. Initial reports comparing Walsh’s approach to its predecessor were promising and demonstrated improved urinary continence (UC). However, subsequent papers have painted a mosaic of results with variable rates of continence dictated by numerous potential confounders [2-9]. Such observations led us to question if NS RP was a clinically significant approach in our own patient population. With the exception of perineural invasion due to significant tumor burden, aggression, or extension, the NS RP is typically championed by urologic surgeons and educated patients [10].

Even if it is successfully performed, the positive effect of NS on postoperative UC is controversial. Some studies from the past decade have emphasized that NS approaches (1) should be performed whenever possible and within clinical reason [8], (2) reduce the time to regained continence [4], and (3) do not adversely affect pathologic outcomes [6]. To contrast, we and others have suggested that there is no significant difference between NS and non-NS procedures regarding long-term continence [5,7,11]. Tzou et al. [5] indicated that the similar outcomes of NNS and NS procedures might be attributable to large differences in data acquisition. Moreover, the heterogeneity of the definitions for continence, and especially for successful NS, further complicates this issue [12].

There is a discrepancy between the “intention to perform” NS and NS that is both successful and effective. Thus, from this, there are 2 possible ways to define NS. One definition is derived from the surgeon’s operative note (surgeon-defined), which is a subjective definition that does not necessarily prove that the essential nerves were successfully spared. A second definition is based on functional outcomes such as preservation of penile erections, which is only possible if the neurovascular bundles (NVB) were themselves preserved. This is an objective way of indicating a successful NS surgery [13,14].

We surmised that if NS did indeed have an effect on continence, then there must be a correlation between potency and continence. Therefore, we hypothesized that the most comprehensive definition of effective NS would be seen in the postoperative recovery of erectile function per the patient International Index of Erectile Function (IIEF)-scores (IIEF-defined). In consideration of the given endpoint of the study, we performed calculations for both surgeon-defined and IIEF-defined NS modalities. Here, we present the results of a prospective investigation on a cohort of patients who underwent RP at our institution over a 9-year period.

MATERIALS AND METHODS

Patient Collective/Cohort
All patients who underwent open RP between January 2004 and January 2013 at the Kantonsspital Baden, Switzerland, were enrolled in the study. During this period, all operations were performed in the same fashion by 5 surgeons; the same senior surgeon was present for all of the operations to provide consistent oversight. Furthermore, the NS step was performed by the senior surgeon in all cases.

Data Acquisition
Functional data was prospectively acquired using self-assessment questionnaires (described below). We also documented clinical and oncological data. Any missing data in the database was later obtained via the patients’ medical records. The database was built using Access and Excel (Microsoft Corp., Redmond, WA, USA).

Self-Assessment Questionnaires
All patients were given a self-assessment questionnaire preoperatively, 3, 9, 12, 18, and 24 months postoperatively, and yearly thereafter. The questionnaire was comprised of 3 sections: (1) the urinary domain of the “Expanded Prostate Cancer Index Composite” (EPIC; discussed below); (2) the IIEF (discussed below); and (3) our institutional Likert system-based questionnaire (also discussed below; used since 1999) to globally assess QoL (Appendix 1).

Expanded Prostate Cancer Index Composite
The EPIC is a well-established and widely used instrument and is comprised of urinary, bowel, and sexual domains [15]. We used the EPIC urinary domain, which consists of 12 questions with 4 to 5 possible answers (symptoms related to obstruction, irritation, and incontinence etc.). Each question was scored on
a scale from 0 to 100. Subscores were summed and averaged to determine a total score for the whole assessment, with higher scores indicating better urinary function [15].

**International Index of Erectile Function**
The IIEF-EF domain is an abbreviated version of the IIEF-15 that pertains specifically to erectile function as well as patient confidence in having and maintaining erections [16]. Specifically, the questionnaire is comprised of items 1, 2, 3, 4, 5, and 15 and is scored out of 30 points; each question is worth 5 points. Scores of 1–10 indicate severe ED, 11–16 indicate moderate ED, 17–21 indicate mild to moderate ED, 22–25 signify mild ED, and 26–30 represent no ED. For the purposes of this study, we state that scores < 11 are 'not potent' and scores ≥11 are 'potent'.

**Quality of Life**
We asked questions concerning different aspects of QoL in the form of an internally developed 7-stepped Likert scale (0–6 points), which conforms to those aspects comprising International Prostate Symptom Score/quality of life questionnaires (Appendix 1).

**Statistical Analysis**
Statistical analysis was performed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA). To determine differences between groups for interval scaled and ordinal variables, we utilized the Mann-Whitney U-test. Categorical variables were appropriately compared using chi-square or Fisher exact tests. For continuous values, the means (with ± standard deviation) or medians (with interquartile range) are given. Kaplan-Meier analysis for the recovery of continence within the follow-up time as well as multivariate Cox regression analyses for the 2 NS definitions (surgeon-defined and IIEF-defined [IIEF-EF ≥ 11]) were used. Hazard ratios were presented with 95% confidence intervals.

**Urinary Continence**
A subgroup of the EPIC score, termed the “EPIC urinary incontinence” (EPIC-Ul), is thought to be the most precise means of describing UI [17]. In an earlier publication, we determined that the optimal COV for “satisfactory continence” was > 85 [12].

**IIEF-Defined NS**
We divided our analysis of IIEF-defined NS outcomes into 2 subgroups: (1) successful NS (henceforth: “NS [EF]”) are all patients who attained an IIEF-EF score of at least 11 during their follow-up, and (2) a group of patients who postoperatively never reached an IIEF of 11 (NNS [EF]). Men with preoperative erectile dysfunction (IIEF-EF < 11) were excluded from further analysis.

**RESULTS**
Between January 2004 and October 2013, 253 men underwent RP at our institution. Seventeen men did not complete preoperative questionnaires and were consequently excluded from the study. All clinical data from the remaining 236 patients were collected and compared. Applying our previously described quantifiable definition of continence (EPIC-Ul > 85), a Kaplan-Meier analysis demonstrated a cumulative continence rate of 76% for the entire cohort. At 1 year postoperatively, 53% recovered satisfactory continence; at 2 years, 61%; and at 3 years, 65%.
Preoperative erectile function appeared to be an important parameter for further analysis. One hundred seventeen patients out of those who underwent surgeon-defined NS RP demonstrated preoperative IIEF-EF scores > 10. Kaplan-Meier analysis revealed that 27% of these patients ultimately did not reach IIEF-EF scores > 10 postoperatively (Fig. 3). Of those who underwent surgeon-defined NNS RP without preoperative ED (i.e., they were considered potent, with IIEF-EF scores > 10), 20% (11 of 55) achieved postoperative IIEF-EF scores > 10.

Collectively, these findings demonstrate a generalized failure rate in the surgeon’s declaration of NS status, giving sufficient reason to attempt a second approach to define NS status utilizing postoperative IIEF scores.
Postoperative IIEF-defined NS RP

Fifty-one men were excluded from our analyses due to preoperative ED (characterized by IIEF-EF scores <11). Still, we wished to determine if these exclusions would have yielded any significant findings; no significant differences in the EPIC-UI scores were observed at any time point between the excluded and remaining populations (Mann-Whitney U-test, P > 0.05). As expected, the mean IIEF-EF scores in the excluded group were significantly lower preoperatively as well as during postoperative follow-up (Mann-Whitney U-test, P < 0.05).

Supplementary Tables 4–6 depict the data at baseline as well as oncologic and functional data during follow-up for postoperative NS. Patients with NNS (EF) were older (65 years [61–67 years] vs. 62 years [56–65 years], P = 0.0007), had a greater tumor stage (pT3: 34% [26 of 77] vs. 19% [22 of 115], P = 0.022) and had a higher grade (Gleason score >7: 31% [24 of 78] vs. 3% [4 of 115], P < 0.0001) as well as higher PSA (6.7 ng/mL [5.43–9.63 ng/mL] vs. 5.4 ng/mL [4.27–6.73 ng/mL], P < 0.0001) at baseline than patients who underwent successful IIEF-defined NS. NNS patients also exhibited a higher rate of macroscopic positive margins (pR2: 10% [8 of 78] vs. 3% [3 of 116], P = 0.024) and positive lymph nodes (pN1: 13% [10 of 78] vs. 2% [2 of 116], P = 0.002) than those who underwent successful IIEF-defined NS.

Influential Factors

Through Kaplan-Meyer analyses, the following factors were found to negatively influence UC recovery and the postoperative time point at which UC was achieved: higher age (≥63 years, which is the median value of the respective Kaplan-Meier curve), positive lymph nodes, higher prostate volume (≥33 g, which is also the median value of the respective Kaplan-Meier curve), clinical high-risk group (RG3 as defined by D’Amico/European Association of Urology risk groups (RGs) 1 & 2, and a table overview of the results shown for each of the graphs. CI, confidence interval; IIEF, International Index of Erectile Function.

Fig. 4. Plots of urinary continence recovery. Hazard ratio (HR) plot of Cox regressions for the recovery of urinary continence (UI-85) as a function of surgeon-defined nerve-sparing (NS) status (A), and IIEF-defined NS status (B), with age (years), prostate volume (mL), European Association of Urology risk groups (RGs) 1 & 2, and a table overview of the results shown for each of the graphs. CI, confidence interval; IIEF, International Index of Erectile Function.
veilance, biochemical recurrence, recurrence-free survival (2 or 5 years), use of androgen deprivation therapy, use of adjuvant radiotherapy, Gleason score (6, 7, and ≥ 8), tumor stage (pathological or clinical), positive margins, and metastasis.

**Multivariate Regression Analyses**

To test the prognosis regarding “recovery of continence” for the complete timeframe, parameters such as NS status, age, prostate volume, and cancer risk group were assessed using the Cox regression in a consolidated model [18]. Lymph node status was excluded due to a congruent representation with the risk group parameter as well as the low number of men with positive status (n = 13). Cox regression analyses with surgeon-defined NS (Fig. 4A) as well as IIEF-defined NS (Fig. 4B) revealed a significant negative influence on postoperative UC for higher age (≥ 63 years) only, but not for NS status.

To achieve maximum comparability, a Cox regression was performed for the binary “no pad” definition of UC as well, with an emphasis on the following factors: age, prostate volume, risk group, and NS (surgeon- and IIEF-defined) status. Neither surgeon- nor IIEF-defined NS statuses demonstrated significant influences on the recurrence of postoperative UC defined by a lack of pad usage (Appendix 2).

**DISCUSSION**

Though the pathogenesis of UI after RP for most patients is based on the presumed intraoperative destruction of the NVB as well as the innervated accompanying muscle tissue, the influence of NS RP on UC preservation remains controversial [3,9,19,20]. Initial reports comparing Walsh’s approach to its predecessor were promising, respectively demonstrating rates of continence as high as 85% versus 16% [21]. Yet, the analysis of over 3 decades’ worth of international NS prostatectomies has yielded a notable mix of results. Flynn and Webster [22] reported a high heterogeneity of outcomes, with post-RP UI spanning the low single-digits up to 74%. To that end, Sanda et al. [2] pointed to age, high PSA scores, and race as factors that affected post-RP UI rates. Reeves and colleagues suggested that NS RP ultimately resulted in earlier recovery of UC but at the 1- and 2-year follow-ups, there was no difference in the rates of continence between those who underwent NS RP versus those who underwent NNS RP [7]. In totality, such studies are highly variable with respect to their data analysis and interpretation [9].

Oftentimes, the available data assessing UI or NS are acquired in different descriptive manners and, at the same time, UI and NS often lack consistent definitions. UI for example, is often defined as being reliant on one or no pads, while NS is usually defined by the surgeon or pathology reports [3-9,12]. However, our study is based on self-reporting questionnaires; here, successful NS is defined by a satisfactory functional outcome regarding erectile function, which proves that the cavernous nerves were maintained and are functional. In another regard, strongly influencing variables such as age have not been recognized in many studies [23]. Lastly, the impact of modern surgical advancements (such as laparoscopic- and robotic-assisted techniques) lack widespread systematic assessment with respect to UI. To this end, a recent publication demonstrated similar functional outcomes between open and robotic-assisted RPs [24].

Kundu et al. [20] assessed the impacts of NS and demonstrated similar results to ours. A positive association was seen between young age and preservation of continence, but none was seen between NS and the prevention of UI [20]. To contrast, Park et al. [6] analyzed a cohort of 360 patients, revealing significantly better UC rates with NS. However, they defined continence as requiring “no pad.” Slight differences from this definition, such as subjectively good continence despite the use of security pads during physical activity, were otherwise classified as “incontinent.” Furthermore, the study utilized only surgeon-defined NS statuses; histologic assessment of functional nerve preservation was not performed, and postoperative potency outcome was not reported. This methodology is congruent to several other studies but not all [3,8,25]. Other studies have defined NS in more unique ways. For example, in addition to using surgeon-defined NS statuses, Tzou et al. [5] performed a subgroup analysis with “successful NS” defined as one that ultimately yielded an erection “firm enough for intercourse.” Of note, this study did not demonstrate any influence of NS on UI. Taking all of this into account, we believe that the controversy surrounding the efficacy of NS RP on UC essentially lies with the definition of continence and the definition of NS. In an attempt to address this, we were the first to use the EPIC scoring system to quantitatively define continence [12]. EPIC allowed us to describe continence in a more nuanced fashion, versus simply relying on the binary definition of “pad” vs. “no pad.” In this study, we expanded upon our quantitative definition of UI by also quantifying the functional outcomes of NS RP using the IIEF scoring system.

A point of distinction between the NNS and NS cohorts is that the NNS group was significantly older and their tumor...
burden significantly larger (Supplementary Tables 2, 5). Traditional wisdom might indicate that an older group with higher tumor burden (receiving NNS surgery) would have impaired continence compared to a younger group with less tumor burden (receiving NS surgery). However, we found no such differences.

To establish a degree of homology with prior work, we also performed a subanalysis using surgeon-defined NS. Here, too, we found no difference in UI rates between either definition of NS and NNS surgery. We also performed a subanalysis using the term "successful NS," but strayed away from defining success based on penile tumescence for intercourse [5]. Instead, we relied upon another clear, widely accepted scoring system — IIEF — to assess potency. In all of these subanalyses, NS did not influence the return or preservation of UC.

Such results are surprising because there is a preponderance of data supporting the NS approach. However, our study demonstrates a different approach to defining "NS," which ultimately impacted how we assessed postoperative outcomes. Additionally, there is a growing body of work that questions the role of the NVB in explicitly innervating the urinary sphincters versus its more clear-cut role in innervating the penis and contributing to potency [26-29]. This is still an area of debate, as a recent publication suggested that the NS technique (and not NVB preservation) was paramount to UC preservation [30].

Strengths of this study include: long follow-up (up to 9 years), largely unchanged, single institution, and single senior surgeon.

On the other hand a corresponding criticism to our single-center status and geographic location would undoubtedly be having a small cohort size. However, the number of patients in our study is comparable in size to several studies [7]. Furthermore, even if significant differences in the postoperative UC of NS and NNS surgeries were seen with higher patient volumes, the clinical relevance of NS surgery would still be called into question.

In conclusion, in this study, we used the IIEF-EF scoring system to objectively measure the postoperative success of NS RP and found that NS RP did not improve postoperative UC. NS surgery conducted with the intent of improving postoperative UC is not necessarily evidence-based. Conservation of UC should not be the primary motivating factor in whether or not a patient and surgeon decide to pursue NS RP and should be highly questioned in the presence of preoperative ED.

SUPPLEMENTARY MATERIALS

Supplementary Tables and Figure can be found via https://doi.org/10.5213/inj.1836052.026.

AUTHOR CONTRIBUTION STATEMENT

- 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: Lukas Hefermehl, Karolin Bossert, Venkat M. Ramakrishnan, Burkhardt Seifert, Kurt Lehmann
- Study concept and design: Lukas Hefermehl, Kurt Lehmann
- Acquisition of data: Lukas Hefermehl, Karolin Bossert, Kurt Lehmann
- Analysis and interpretation of data: Lukas Hefermehl, Karolin Bossert, Venkat M. Ramakrishnan, Burkhardt Seifert, Kurt Lehmann
- Drafting of the manuscript: Lukas Hefermehl, Karolin Bossert, Venkat M. Ramakrishnan, Burkhardt Seifert, Kurt Lehmann
- Critical revision of the manuscript for important intellectual content: Venkat M. Ramakrishnan, Burkhardt Seifert
- Statistical analysis: Lukas Hefermehl, Karolin Bossert, Burkhardt Seifert
- Study supervision: Lukas Hefermehl, Kurt Lehmann

REFERENCES


7. Reeves F, Preece P, Kapoor J, Everaerts W, Murphy DG, Corcoran


### Appendix 1. Quality of life questionnaire

1. How would you describe your overall quality of life?

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<th>Satisfied</th>
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2. How would you describe your quality of life regarding the changes due to your disease?

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3. How content are you with your urinary continence?

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4. How would you describe the quality of your sexuality?

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5. How would you describe the quality of your partnership?

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6. How satisfied are you with your social life (for e.g., going out, friends, hobbies)?

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Appendix 2. Hazard ratio (HR) plots of the Cox regressions for the recovery of continence (no pad)

Hazard ratio (HR) plots of the Cox regressions for the recovery of continence (no pad) as a function of the following factors: (A) Surgeon- and (B) IIEF-defined nerve-sparing (NS), with both plots also showing age (years), prostate volume (mL), European Association of Urology risk groups (RGs) 1 & 2, and table overviews of the results. CI, confidence interval; IIEF, International Index of Erectile Function.