The Effect of Nerve Sparing Status on Sexual and Urinary Function: 3-Year Results from the CEASAR Study

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Purpose: Nerve sparing contributes to the recovery of sexual and urinary function after radical prostatectomy but it may be ineffective in some patients or carry the risk of a positive surgical margin. We evaluated sexual and urinary function outcomes according to the degree of nerve sparing in patients with prostate cancer treated with radical prostatectomy.

Materials and Methods: The CEASAR (Comparative Effectiveness Analysis of Surgery and Radiation) study is a prospective, population based, observational study of men diagnosed with localized prostate cancer in 2011 to 2012. Patient reported sexual and urinary functions were measured using the 26-item EPIC (Expanded Prostate Index Composite) at baseline within 6 months after diagnosis, and 6, 12 and 36 months after enrollment. Study inclusion criteria included radical prostatectomy as primary treatment, documentation of nerve sparing status and absent androgen deprivation therapy. Nerve sparing status was defined as none, unilateral or bilateral according to the operative report.

Results: The final analytical cohort included 991 men. The 11 men treated with unilateral nerve sparing and the 75 treated with a nonnerve sparing procedure were grouped together. In the multivariable model there was a significant difference in the sexual function score 3 years after radical prostatectomy in the

Abbreviations and Acronyms

BNS = bilateral nerve sparing

CaPSURE™ = Cancer of the Prostate Strategic Urologic Research Endeavor

CEASAR = Comparative Effectiveness Analysis of Surgery and Radiation

EPIC = Expanded Prostate Index Composite

NNS = nonNS

NS = nerve sparing

PROSTQA = Prostate Cancer Outcomes and Satisfaction With Treatment Quality Assessment

RP = radical prostatectomy

TIBI-CaP = Total Illness Burden Index for Prostate Cancer

UNS = unilateral NS

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bilateral nerve sparing group compared with the unilateral and nonnerve sparing group (6.1 points, 95% CI 2.0 10.3, p = 0.004). This was more pronounced in men with high baseline sexual function (8.23 points, 95% CI 1.6 14.8, p = 0.014) but not in those with low baseline function (4.0 points, 95% CI 0.6 8.7, p = 0.090). Similar effects were demonstrated on urinary incontinence scores.

Conclusions: Bilateral nerve sparing resulted in better sexual and urinary function outcomes than unilateral or no nerve sparing but the difference was not significant in men with low baseline sexual function.

Key Words: prostatic neoplasms, prostatectomy, recovery of function, urination disorders, erectile dysfunction

PRESERVATION of the neurovascular bundles influences the recovery of sexual function after RP for localized prostate cancer.[1] This has been demonstrated consistently in numerous studies.[2 8] In the PROSTQA study NS was associated with erection recovery at 2 years compared to nonNS RP.[9] However, some men who undergo RP may lack the potential to regain sexual function even if NS is performed.

Factors that contribute to the recovery of sexual function among men who undergo RP include age, prostate size, comorbidity, prostate cancer risk, NS status, surgeon experience, baseline sexual function and race. However, men with low baseline sexual function have a low likelihood of regaining sufficient function, raising the question of whether NS is indicated in this group.[9,10] There is evidence that NS improves urinary incontinence outcomes and at least the theoretical risk of positive surgical margins in men who undergo NS compared to nonNS.[11 16] However, the potential benefits of contemporary RP and its effects on sexual function and urinary incontinence have not been studied thoroughly in men with high and low baseline sexual function.

Thus, we evaluated the effect of NS on 3-year postoperative sexual and urinary function outcomes in a contemporary population based cohort and to determine how patient specific and surgeon specific factors mitigate the benefits of NS. We hypothesized that men with low baseline sexual function would experience minimal benefit from NS in sexual or urinary function recovery.

METHODS

Analytical Cohort

Data were obtained from CEASAR. That study accrued 3,269 men younger than 80 years diagnosed with localized prostate cancer in 2011 and 2012 within 6 months who had prostate specific antigen less than 50 ng/ml, from 5 SEER (Surveillance, Epidemiology and End Results) registry catchment areas, including Louisiana, New Jersey, Utah, Atlanta and Los Angeles, and from the CaPSURE™ cohort.[17] Of the 3,269 enrolled men 991 met study inclusion criteria, including RP as primary treatment, no receipt of androgen deprivation therapy and documentation of NS in the operative report (supplementary fig. 1, http://jurology.com/). A unique aspect of CEASAR is the inclusion of patients on the study team, in accordance with funding from PCORI (Patient Centered Outcomes Research Institute).

Detailed methods were previously described.[18] Institutional review board approval was obtained from the coordinating center and each study site Informed consent was obtained from all participating patients.

Data Collection

Patient reported sexual and urinary function was captured using the 26-item EPIC questionnaire, a validated instrument with domains scored on a range 0 to 100 with higher scores indicating better function.[19] Surveys were collected at baseline, and 6, 12 and 36 months after study enrollment. Previously published and validated domain score thresholds representing minimally important differences in EPIC domain scores were used in data interpretation.[20] Participants also completed TIBI-CaP, a validated, patient reported, 84-item comorbidity assessment specific for patients with prostate cancer with a score range of 0 to 23 with lower scores indicating fewer or less severe comorbidities.[21 22] Demographics and validated questionnaires for cancer related anxiety[23] and depression[24] were also collected. Tumor characteristics, NS degree defined as NNS, UNS or BNS according to the operative report, prostate specific antigen levels and treatment date were obtained via medical record abstraction.

Statistical Analysis

We compared the baseline characteristics of patients with known and unknown NS status, and found no major differences (supplementary table 1, http://jurology.com/). On sensitivity analyses and in exploratory models we included NNS, UNS and BNS as 3 separate groups (supplementary tables 2 and 3 and supplementary fig. 2, http://jurology.com/). From these analyses we found that the UNS and NSS groups were similar in most baseline characteristics and in postoperative sexual function scores. We combined the UNS and NNS groups for comparison with BNS in our primary analyses based on this analysis and on evidence from historical studies showing that UNS and NNS outcomes are more similar to each another than they are to BNS.[6,25,26] Patient demographic and baseline characteristics were summarized by NS status. Differences between the UNS/NNS and BNS groups were compared by the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables.

We evaluated the effect of NS on sexual and urinary function outcomes using EPIC sexual function and

urinary incontinence domain scores, and single item responses. We selected single items to highlight issues of particular importance to patients. Responses for analysis were dichotomized as sexual and urinary function bother—no, very small or small problem vs moderate or big problem, erection firmness—firm enough for intercourse vs less and incontinence pad use—none vs 1 or more per day.

To display trajectory plots of average sexual and urinary function with time we fit linear regression models using ordinary least squares to predict EPIC domain scores as a function of time since treatment according to NS status, age group (40 to 60, 61 to 70 and 71 to 80 years) and baseline sexual function (low and high), incorporating function scores from each time point. We dichotomized baseline sexual function at its median value (EPIC sexual function domain score less than 80 vs 80 or greater) to simplify the presentation.

To assess associations between NS status and each outcome measure at the 3-year time point we fit linear regression models (sexual and urinary incontinence domain scores) and logistic regression models (individual items). Restricted cubic splines of time since treatment were used to allow for nonlinear relationships between time and outcome. Robust covariance matrix estimates by the Huber-White method were used to account for potential correlation among multiple records pertaining to the same individual at different time points.

All multivariable models included age, race (black or nonblack), disease risk stratum at baseline (D'Amico low, intermediate or high),[27] postoperative erectile aid use (yes or no), having a sexual partner at baseline (yes or no), TIBI-CaP (0 to 2, 3 to 6, or 7 or more), depression using CES-D (Center for Epidemiological Studies-Depression), the prostate cancer specific worry score and corresponding baseline domain scores. Clinicians and patients on the study team selected these covariates a priori based on clinical relevance and significance in prior studies. We also included an estimate of surgeon experience by calculating each surgeon volume in the CEASAR cohort during the 13-month accrual period, including 1 to 3 (28%), 4 to 10 (36%) or greater than 10 cases (36%). The models included interaction terms for baseline sexual function and NS status to determine whether the effect of NS differed by baseline function status.

Multiple imputation was used for missing covariate values. Statistical significance was considered for all 2-sided p values of 5% or less. All analyses were done with R, version 3.3 (https://www.r-project.org/).

RESULTS

The analytical cohort included 991 men, of whom 80% underwent the robotic approach while 19% and 1% were treated with an open or other approach, respectively. The response rate was 98% at 6 months, 96% at 12 months and 88% at 36 months, and it was similar in the 2 groups. The table lists baseline demographic and clinical characteristics by the degree of NS. [T1]

On unadjusted analyses of a priori selected subgroups higher sexual and urinary incontinence domain scores after prostatectomy appeared to be associated with younger age, high baseline sexual function, BNS, lower comorbidity scores and lower disease risk. Figure 1 shows a trajectory plots of sexual function and urinary incontinence domain scores as a function of time, stratified by NS degree, age and baseline sexual function. [F1]

Outcomes

Sexual Function. On multivariable analysis younger patient age and lower comorbidity were significantly associated with higher 3-year sexual domain scores while race, D'Amico risk and surgeon volume were not (fig. 2). In exploratory models the interaction between surgeon volume and NS status was not statistically significant (data not shown). [F2]

There was a statistically significant benefit of BNS compared to UNS/NNS (6.1 points, 95% CI 2.0 10.3, p = 0.004). The effect of BNS was significant in men with high baseline function (8.2 points, 95% CI 1.6 14.8, p = 0.014) but it was attenuated in men with low baseline function (4.0 points, 95% CI 0.6 8.7, p = 0.09, fig. 2). These effects were also seen for individual item question responses to erection sufficient for intercourse and sexual bother (supplementary fig. 3, http://jurology.com/).

Urinary Incontinence. On multivariable analysis younger age, nonblack racial group and BNS were associated with better urinary incontinence scores 3 years after surgery (fig. 3). However, much like sexual function, the benefit of BNS on the urinary incontinence score was pronounced in men with high baseline sexual function (7.5 points, 95% CI 1.4 13.6, p = 0.015). The difference between BNS and UNS/NNS was not significant in men with low baseline sexual function (2.1 points, 95% CI 3.6 7.8, p = 0.48, fig. 3). A similar effect was seen for urinary function bother but not for the report of using 1 pad or more per day (supplementary fig. 4, http://jurology.com/). [F3]

Surgical Margin Status

Of the 186 patients treated with NNS/UNS 40 had positive surgical margins (22.3%) vs 172 of the 805 men (21.8%) who underwent BNS (p = 0.87). On multivariable regression controlling for disease risk factors the OR of a positive surgical margin for BNS vs NNS/UNS was 1.08 (95% CI 0.72 1.60, p = 0.72).

DISCUSSION

In this population based study we explored how patient factors influenced the effect of NS status in a community setting. We found that BNS was associated with recovery of sexual function and urinary incontinence scores 3 years after surgery for localized prostate cancer. While we noted a statistically

Demographic and clinical characteristics by nerve sparing status

		Nerve Sparing						
	No. Pts	Unilat/None		Bilat		Unilat/None + Bilat		p Value
Overall	991	186		805		991		—
Median age at diagnosis (IQR)	991	63	(58–67)	61	(56–66)	62	(57–66)	0.019
No. race (%):	983							0.029
White		137	(74)	633	(79)	770	(78)	
Black		31	(17)	71	(9)	102	(10)	
Hispanic		10	(5)	61	(8)	71	(7)	
Asian		5	(3)	20	(3)	25	(3)	
Other		2	(1)	13	(2)	15	(2)	
No. education (%):	964							0.004
Less than high school		21	(12)	52	(7)	73	(8)	
High school graduate		44	(25)	144	(18)	188	(20)	
Some college		46	(26)	178	(23)	224	(23)	
College graduate		37	(21)	194	(25)	231	(24)	
Graduate/professional school		31	(17)	217	(28)	248	(26)	
Median prostate Ca related anxiety (IQR)	980	35.7	(17.9–53.6)	28.6	(17.9–46.4)	32.1	(17.9–46.4)	0.006
Median CESD depression (IQR)	974	14.8	(3.7–29.6)	14.8	(3.7–29.6)	14.8	(3.7–29.6)	0.405
Median EPIC 26 baseline sexual function score (IQR)	950	75.0	(37.1–95.0)	80.0	(53.3–95.0)	80.0	(48.3–95.0)	0.138
No. baseline sexual function (%):	950							0.369
Low		86	(51)	365	(47)	451	(47)	
High		84	(49)	415	(53)	499	(53)	
Median baseline EPIC 26 urinary incontinence domain score (IQR)	962	100.0	(79.2–100.0)	100.0	(84.5–100.0)	100.0	(82.3–100.0)	0.302
No. baseline erectile aids (%):	991							0.527
No		134	(72)	561	(70)	695	(70)	
Yes		52	(28)	244	(30)	296	(30)	
No. TIBI CaP (%):	969							0.198
0–2		63	(35)	274	(35)	337	(35)	
3–6		103	(57)	479	(61)	582	(60)	
7 or More		14	(8)	36	(5)	50	(5)	
No. D'Amico risk group (%):	990							<0.001
Low		45	(24)	394	(49)	439	(44)	
Intermediate		99	(53)	322	(40)	421	(43)	
High		42	(23)	88	(11)	130	(13)	
No. cases surgeon vol (%):	843							0.129
1–3		47	(30)	186	(27)	233	(28)	
4–10		64	(41)	237	(35)	301	(36)	
Greater than 10		47	(30)	262	(38)	309	(37)	
No. pos surgical margin (%)	805	40	(22)	172	(22)	212	(21)	0.953

significant difference in 3-year sexual domain scores between BNS and UNS/NNS, the magnitude of difference in scores was smaller than the proposed threshold of clinical significance (10 to 12 points).[20] When stratified by baseline sexual function, the difference between BNS and UNS/NNS sexual domain scores approached clinical significance in men with high baseline function but a smaller and nonsignificant difference was noted in men with low baseline function. We found a similar effect of BNS and UNS/NNS in the 3-year urinary incontinence domain scores. Clinical significance (6 to 9 points)[20] was reached in men with high baseline sexual function but not in men with low baseline sexual function.

PROSTQA, a previous multi-institutional study, demonstrated that NS was associated with the sexual function outcome but since only 41 of 603 men underwent NNS surgery, the finding failed to achieve statistical significance ($p = 0.08$).[3] In a followup study of PROSTQA Alemozaffar et al created a predictive model of patient pretreatment characteristics, which demonstrated that age, baseline sexual function and NS status all predicted erectile function recovery.[9] These results are representative of men treated at centers of excellence by university affiliated urologists and they may not be generalizable at the population level.

PCOS (Prostate Cancer Outcomes Study), the only population based study to assess the effect of BNS, demonstrated that men treated with NNS RP had a higher rate of impotence 18 months or longer after RP (66% vs 56%, $p = 0.001$). However, this comparison included only men with high baseline sexual function and all RPs in PCOS were done via an open approach as the study predated the advent of robotic assisted RP.[5] In a study of the CaPSURE database Harris et al found a statistically significant benefit of BNS in men with high baseline sexual function but not in men in the lowest quartile of baseline sexual function.[11] This is similar to our study finding.

Interestingly the magnitude of difference in sexual function scores between the BNS and UNS/NNS groups in our study was smaller than one would expect from prior studies. Previous investigators reported that the proportion of men

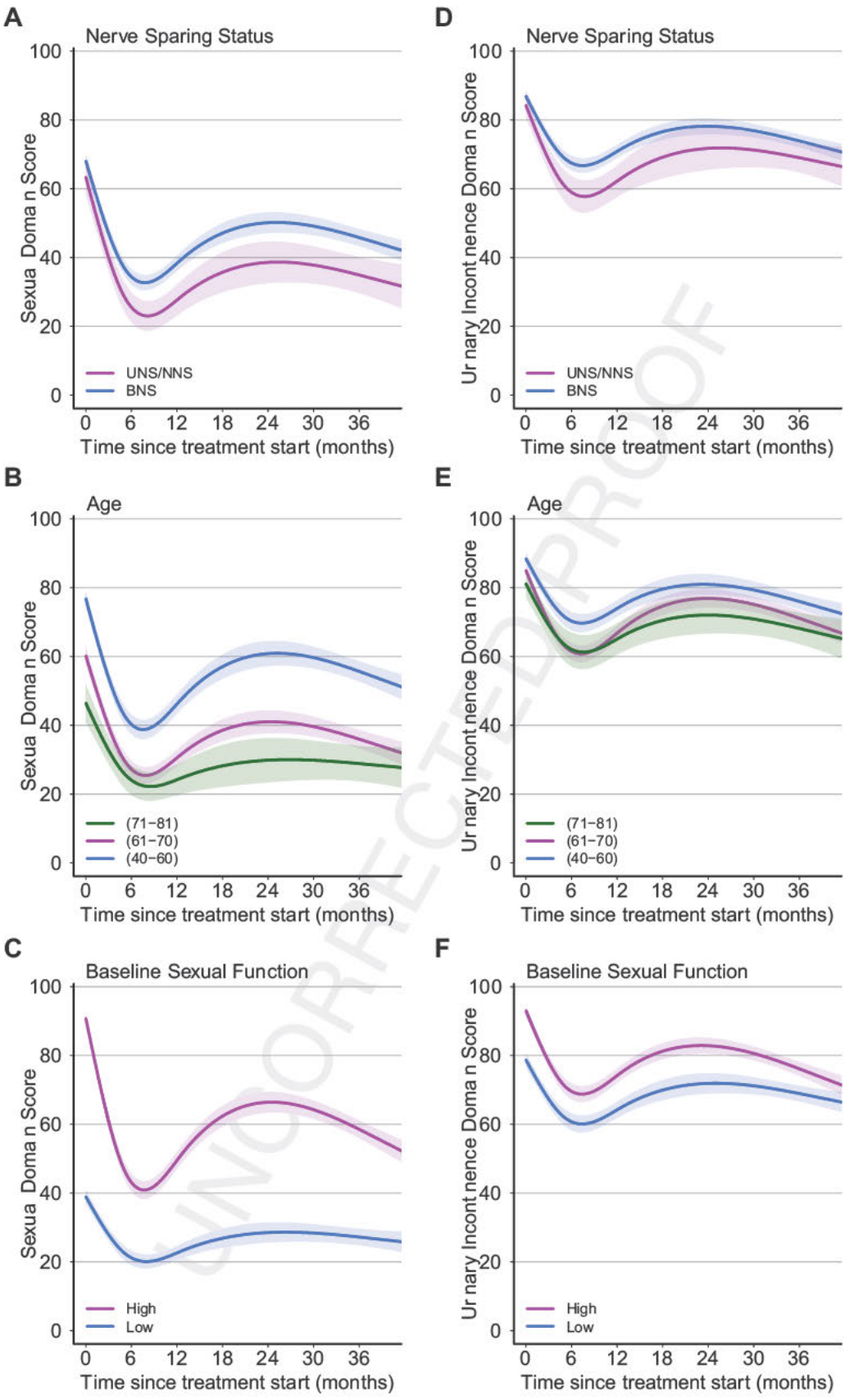

Figure 1. Unadjusted trajectory plots of sexual function (*A* to *C*) and urinary incontinence (*D* to *F*) EPIC 26 domain scores as function of time stratified by degree of NS, age and baseline sexual function.

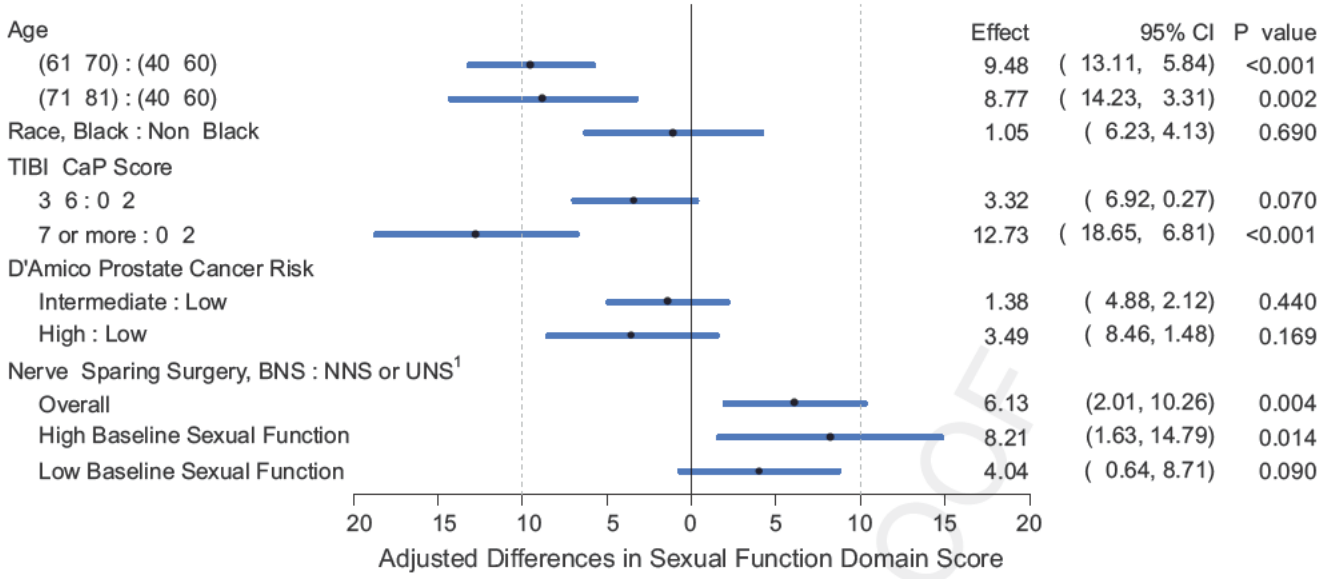

Figure 2. Adjusted differences in sexual function domain score

who achieved potency by 1 year ranged from 38% to 91% for BNS, 33% to 71% for UNS and 10% to 62% for NNS.[4,7,8,26,28 30] The reasons for such heterogeneity and for the apparent discrepancy between our study and previous studies include different assessments of erectile function, varying types of NS procedures, patient selection bias (including only men with preoperative potency) or highlighting results from centers of excellence. In addition, information bias could affect comparisons of our study with others. In particular we ascertained NS status from operative reports, which may be a less reliable data source than the sources used in other studies.

Our finding that NS was not associated with improved urinary function outcomes in men with low baseline sexual function runs counter to previous studies. For example, a CaPSURE study showed that BNS was associated with improved urinary function scores in men in the lowest quartile of baseline sexual function.[11] The investigators hypothesized that poor preoperative vascular status may have contributed to poor baseline function in the sexual and urinary domains. They advocated for NS in men

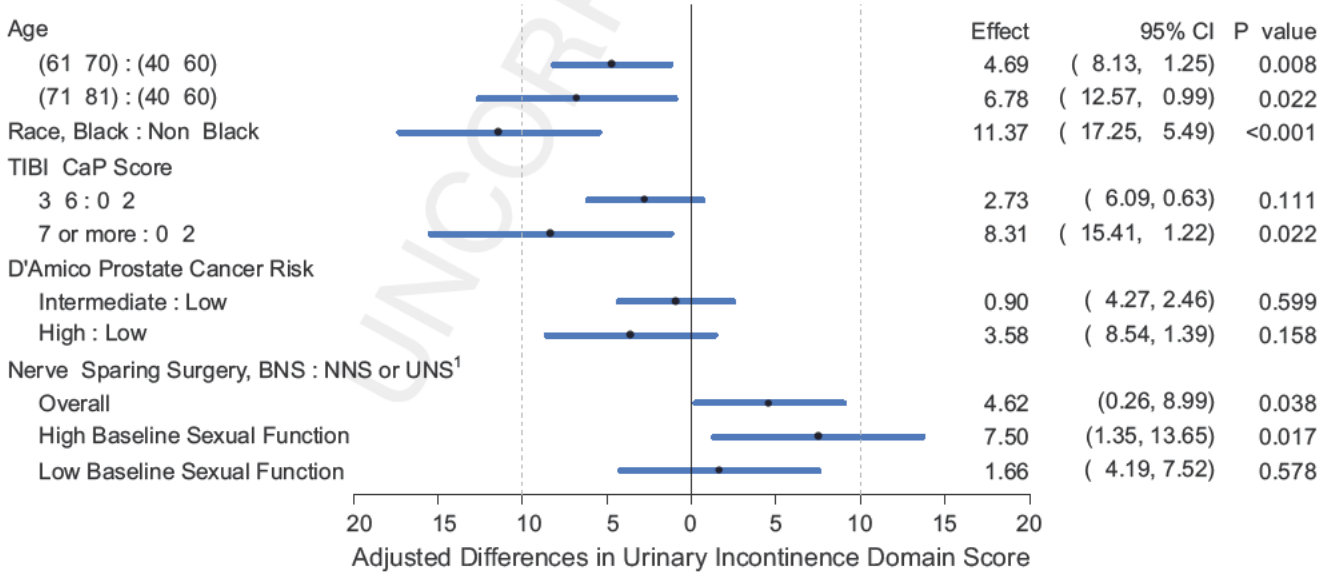

Figure 3. Adjusted differences in urinary incontinence domain score

with poor baseline sexual function to facilitate the recovery of urinary function. In our study BNS did not improve urinary function scores in men with poor baseline sexual function. The reasons for this discrepancy are not clear. In general the association between NS and continence, and the groups that may benefit in that regard require further study.

Findings of our study should be interpreted in light of its strengths and limitations. A limitation was ascertaining NS status from operative reports. NS status was missing in 28% of the patients and they were omitted from study, although our descriptive analysis of missing values did not detect any major differences. Furthermore, we did not assess the quality of NS data documented in operative reports so that possible misclassification bias cannot be ruled out. Although surgeons have no financial incentive to document NS when it was not performed, they may have been apt to dictate a case as BNS even when NS was not thorough or complete. Such misclassification would tend to diminish the difference between the BNS and UNS/NNS groups, and would have biased the results toward the null rather than inflating our results.

In addition, a limited number of patients underwent NNS or UNS, which limited our ability to precisely and robustly estimate the effects of UNS on outcomes in comparison with NNS. However, our sensitivity analyses demonstrated similarities between UNS and NNS, and support our clinical rationale in combining UNS with NNS in the primary analyses. Combining UNS and NNS would also tend to have biased our results toward the null.

Major strengths of our study include the population based sample, the longitudinal design which enabled allowed analyses of repeat measures and relatively recent data in which most patients had undergone contemporary robotic surgery.

We identified a subgroup of patients who benefited clinically from BNS, that is men with high baseline sexual function. NS did not appear to improve sexual function or urinary incontinence outcomes in men with low baseline sexual function. Given the potential risk of positive surgical margins that accompanies nerve sparing (although we failed to find one), our findings suggest that men with low baseline sexual function who elect radical prostatectomy should be considered for NNS surgery.

As we refine our decision making about which patients should undergo NS, it is important to acknowledge that 44% of the men who underwent surgery did so for low risk disease, which could have been observed instead.

CONCLUSIONS

In a contemporary practice BNS appeared to have the most benefit in men with high baseline sexual function but it may be over performed in men with poor baseline sexual function. These findings should be strongly considered when counseling men regarding treatment outcomes.

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