Nerve Sparing during Robot-Assisted Radical Prostatectomy Increases the Risk of Ipsilateral Positive Surgical Margins

T. F. W. Soeterik,* H. H. E van Melick, L. M. Dijksman, S. Stomps, J. A. Witjes and J. P. A. van Basten

From the Department of Value-Based Healthcare (TFWS), Santeon, Utrecht, Department of Urology (HHEvM) and Department of Value-Based Healthcare (LMD), St. Antonius Hospital, Nieuwegein-Utrecht, Department of Urology, Hospital Group Twente, Almelo-Hengelo (SS), Department of Urology, Radboud University Nijmegen Medical Centre (JAW) and Department of Urology, Canisius Wilhelmina Hospital (JPAvB), Nijmegen, The Netherlands

Purpose: Available published studies evaluating the association between nerve sparing robot-assisted radical prostatectomy and risk of ipsilateral positive surgical margins were subject to selection bias. In this study we overcome these limitations by using multivariable regression analysis.

Materials and Methods: Patients undergoing robot-assisted radical prostatectomy for prostate cancer at 4 institutions from 2013 to 2018 were included in the study. A multilevel logistic random intercept model, including covariates on patient level and side specific factors on prostate lobe level, was used to evaluate the association between nerve sparing and risk of ipsilateral positive margins.

Results: A total of 5,148 prostate lobes derived from 2,574 patients who underwent robot-assisted radical prostatectomy were analyzed. Multivariable analysis showed nerve sparing was an independent predictor for ipsilateral positive margins (OR 1.42, 95% CI 1.14–1.82). Other significant predictors for positive margins were prostate specific antigen density (OR 3.64, 95% CI 2.36–5.90) and side specific covariates including highest preoperative ISUP (International Society of Urological Pathology) biopsy grade (OR 1.58, 95% CI 1.13–2.53; OR 1.62, 95% CI 1.13–2.69; OR 2.11, 95% CI 1.39–3.59 and OR 4.43, 95% CI 3.17–10.12 for ISUP grade 2, 3, 4 and 5, respectively), presence of extraprostatic extension on magnetic resonance imaging (OR 1.42, 95% CI 1.03–1.91) and percentage of positive cores on systematic biopsy (OR 3.82, 95% CI 2.50–5.86).

Conclusions: Nerve sparing was associated with an increased risk of ipsilateral positive surgical margins. The increased risk of positive margins should be considered when counseling patients who opt for nerve sparing robot-assisted radical prostatectomy.

Abbreviations and Acronyms

DRE = digital rectal examination
EPE = extraprostatic extension
ISUP = International Society of Urological Pathology
MRI = magnetic resonance imaging
PSA = prostate specific antigen
PSAD = prostate specific antigen density
RARP = robot-assisted radical prostatectomy
RP = radical prostatectomy
TRUS = transrectal ultrasonography

Accepted for publication January 17, 2020.
Supported by Astellas Pharma and Amgen.
No direct or indirect commercial, personal, academic, political, religious or ethical incentive is associated with publishing this article.

* Correspondence: Koekoekslaan 1, 3435 CM, Nieuwegein, The Netherlands (email: t.soeterik@antoniusziekenhuis.nl).

Key Words: prostatic neoplasms, prostatectomy, margins of excision, outcomes

RADICAL prostatectomy is a treatment modality for localized prostate cancer shown in a prospective randomized trial to significantly increase life expectancy compared with conservative management.[1] Together with radiation therapy it is one of the most established treatment options for patients with localized prostate cancer and a life expectancy greater than 10 years.[2]

Erectile dysfunction and urinary incontinence are unfortunately common consequences of RP that have a severe impact on quality of life, affecting approximately 80% and 20% of patients, respectively.[3,4] Preservation of the neurovascular bundles can potentially decrease the risk of erectile dysfunction and to a lesser extent urinary incontinence.[5,6] Because the

0022-5347/20/2041-0091/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000000760
Vol. 204, 91-95, July 2020
Printed in U.S.A.

neurovascular bundles are adjacent to the prostate, it is highly possible that nerve sparing comes with an increased risk of positive surgical margins.

Although the European Association of Urology guidelines state that nerve bundle preservation is contraindicated in case of tumors with a high risk of extracapsular disease, it is assumed that it can be performed safely in most men with localized disease.[2] A systematic review and meta-analysis confirmed the safety of nerve sparing in patients with localized prostate cancer, as it was not associated with an increased risk of positive margins among patients with pT2 tumors (RR 0.92, 95% CI 0.715−1.13). Remarkably, in patients with pT3 disease nerve sparing was even associated with a decreased risk of positive margins (RR 0.83, 95% CI 0.71−0.96).[7] However, these results should be interpreted with caution as the observational studies previously performed on this subject are susceptible to selection bias.

The available published studies that support current guidelines may have insufficiently accounted for case mix differences due to patient selection. Therefore, these confounders may have consequently masked the actual association between nerve sparing and the risk of positive margins. Since a positive margin is associated with a higher risk of biochemical recurrence and even cancer specific mortality,[8,9] proper surgical planning for nerve sparing with a minimum risk of positive margins should be undertaken.

Given the importance of the issue and the limitations of the previous research, a need remains for studies of higher methodological quality on this subject. Obviously a randomized controlled trial would be the most methodologically sound approach. However, randomizing patients for nerve sparing and nonnerve sparing surgery would not likely be done based on ethical grounds as assignment to nonnerve sparing could be regarded as unnecessarily harmful for patients randomized into the nonnerve sparing arm. As there are several studies reporting the benefits of nerve sparing during RP, these patients will not have the opportunity to retain erectile function.[10] Therefore, the aim of this study is to evaluate the association between nerve sparing RP and the risk of a positive surgical margin by retrospectively analyzing a large multicenter patient population, adjusting for a large number of patient related and prostate side specific covariates using multivariable regression analysis.

PATIENTS AND METHODS

Patients and Data Collection

Patients diagnosed with prostate cancer undergoing robot-assisted radical prostatectomy as primary treatment at 4 Dutch teaching hospitals (Martini Hospital Groningen, Hospital Group Twente, St. Antonius Hospital Nieuwegein/Utrecht and the Canisius Wilhelmina Hospital Nijmegen) from 2013 to 2018 were included in the study (IRB No. Z18.023). Data were captured in a prospective manner. Patients were excluded from analysis if they underwent salvage RARP or were treated with up-front androgen deprivation therapy. Baseline characteristics (age, clinical T stage based on DRE, radiological T stage based on MRI, preoperative serum PSA, total biopsy cores taken and number of positive cores at diagnosis, Gleason score, prostate volume measured using TRUS or MRI), treatment information (date of surgery, surgeon, nerve sparing as mentioned in the surgical report) and definitive pathology data (pathological T stage, Gleason score, margin status) were documented. In addition, prostate side specific radiological, surgical and pathological data were retrospectively collected.

Predictor and Outcome Definitions

The most recent preoperative PSA and prostate volume measured by TRUS or MRI were used to calculate PSAD (serum PSA [ng/ml] divided by prostate volume [ml]). DRE was subdivided into the 3 stages of T1 (benign), T2 (nodule) or T3 (EPE). All radical prostatectomies performed in the study period were robot-assisted. Interfascial nerve sparing was performed using an antegrade approach. After the upward traction of vas and seminal vesicles, the prostatic pedicle was observed and controlled athermally at the base of the prostate. Then the prostate was pulled to the opposite side and the lateral pelvic fascia was exposed. The triangular space between the lateral pelvic fascia, Denonvilliers' fascia and the prostate was observed and the neurovascular bundle was defined. Subsequently the lateral pelvic fascia was exposed and the interfascial dissection was performed. The nonnerve sparing technique included dissection posterior to Denonvilliers' fascia and incision on to the perirectal fat lateral to the neurovascular bundles.

RARP was performed by 14 surgeons. Surgical experience per surgeon varied from 0 procedures (least experienced) to 500 procedures (most experienced) at the beginning of the study period. For the analysis the most experienced surgeon was used as the reference category. Prostatic carcinoma was graded using the 2014 ISUP grading system.[11] A positive surgical margin, assessed by dedicated uropathologists, was defined as tumor cells present at the inked margin.[12]

Statistical Analysis

Each prostate lobe was considered a separate case. A multilevel regression model was used to evaluate the association between nerve sparing and positive surgical margins. Side specific factors included nerve sparing, DRE, MRI local stage (organ confined vs EPE), highest ISUP grade found on biopsy and percentage of positive cores. Covariates available on patient level included PSAD, surgeon, hospital and age. To adjust for the consequential data clustering on patient level a random intercept was included in the model. Missing data were assumed to be missing at random, based on the missing data patterns, and were imputed using multiple imputations.[13] Analysis was performed using R Studio.[14]

RESULTS

Study Population

A total of 2,574 patients underwent RARP from 2013 to 2018 at the 4 hospitals. The baseline characteristics and surgical outcomes of these patients are presented in supplementary tables 1 and 2 (https://www.jurology.com). Positive surgical margin rates were observed in 844 (33%) of 2,574 cases. The positive margin rate was 23% in pT2 (353 of 1,533) and 47% in pT3 or greater (491 of 1,041) tumors. A total of 1,755 (68%) patients underwent interfascial nerve sparing surgery (unilateral or bilateral).

Nerve Sparing vs Nonnerve Sparing

Nerve sparing status was not available in 97 patients and, thus, could not be categorized. Baseline characteristics of 4,954 prostate lobes of the remaining 2,477 patients with known nerve sparing status are presented in supplementary table 3 (https://www.jurology.com). In general the nerve sparing group had more favorable tumor characteristics compared to the nonnerve sparing group.

Missing Data

Of the 2,574 patients who underwent RARP during the study period data relevant for analysis were missing in 889. This was mainly attributable to the fact that 364 patients (14%) did not undergo preoperative MRI and 263 (10%) underwent targeted biopsies without systematic biopsies. Thus, radiological T stage and prostate side specific percentage of positive cores were not available in these cases. In addition, prostate volume was not determined using TRUS or MRI in 86 (3%) cases. Extensive information regarding missing data is given in a patient flow chart (supplementary figure, https://www.jurology.com).

Evaluation of Predictors for Positive Surgical Margins

The results of the multivariable analysis predicting positive margins are presented in the table. Model 1 included solely complete cases. Additional analysis was done after accounting for missing data using multiple imputation (model 2). Overall, model 2 resulted in more precise estimation of coefficients, with narrower 95% confidence intervals compared with the complete case analysis (model 1). In both models nerve sparing was associated with significantly higher ORs of ipsilateral positive margins. Other covariates found to be significant predictors for positive margins in models 1 and 2 were PSAD, highest ipsilateral biopsy ISUP grade 2 and higher, percentage of positive cores on systematic biopsy and presence of EPE on preoperative multiparametric MRI.

DISCUSSION

In this study we explored the association between side specific nerve sparing RP and the risk of ipsilateral positive margins using a large, multi-institutional, real-world patient cohort. On multivariable logistic regression analysis nerve sparing was associated with significantly higher odds of positive margins

Multivariable logistic regression analysis predicting positive surgical margins

	Model 1 (3,325) OR (95% CI)*	p Value	Model 2 (5,148) OR (95% CI)†	p Value
Age	0.98 (0.96–1.0)	0.038	0.98 (0.97–1.00)	0.11
PSAD	2.72 (1.57–4.72)	<0.001	3.64 (2.36–5.90)	<0.001
ISUP grade:				
Benign	Referent		Referent	
1	1.15 (0.79–1.68)	0.5	1.24 (0.93–1.81)	0.2
2	1.48 (0.97–2.27)	0.069	1.58 (1.13–2.53)	0.015
3	1.65 (0.99–2.73)	0.053	1.62 (1.13–2.69)	0.037
4	2.09 (1.20–3.66)	0.01	2.11 (1.39–3.59)	0.002
5	5.56 (2.90–10.63)	<0.001	4.43 (3.17–10.12)	<0.001
DRE:				
T1	Referent		Referent	
T2	1.33 (0.99–1.79)	0.062	1.21 (0.93–1.62)	0.17
T3	1.45 (0.81–2.60)	0.2	1.66 (0.93–3.01)	0.075
MRI stage:				
Organ confined	Referent		Referent	
EPE	1.48 (1.05–2.07)	0.024	1.42 (1.03–1.91)	0.031
% Pos cores	3.50 (2.23–5.49)	<0.001	3.82 (2.50–5.86)	<0.001
Nerve sparing:				
Nonnerve sparing	Referent		Referent	
Nerve sparing	1.53 (1.15–2.03)	<0.001	1.42 (1.14–1.82)	0.005

The analysis also included the covariates hospital (4) and surgeon (14). ORs are not shown.
* Complete case analysis.
† Imputed case analysis using multiple imputations.

compared with nonnerve sparing (OR 1.42, 95% CI 1.14−1.82). Our study results call into question the classic suggestion that nerve sparing is not associated with an increased risk of positive surgical margins.

Our main findings are relevant for clinical practice as patients and their urologists need to be aware of the fact that nerve sparing does increase the risk of positive margins. This effect was masked in previous studies, apparently due to methodological limitations and insufficient unadjusted residual confounding by indication. Also, as nerve sparing does not guarantee preservation of erectile function,[10] patients unlikely to benefit from nerve sparing should not be unnecessarily exposed to its risks.

Several studies on this topic have been performed previously, reporting conflicting results. Coelho et al reported comparable positive margin rates of 876 patients regardless of nerve sparing type.[15] For bilateral, unilateral and nonnerve sparing, respectively, the positive margin rates in pT2 tumors were 8.2%, 6.1% and 8.5% ($p=0.93$) and 27.7%, 26.7% and 30.8% ($p=0.93$) in pT3. Comparable findings were reported in a study by Moore et al, including 945 patients.[16] The authors reported no significant differences in positive margin rates between nerve sparing groups on multivariable analysis adjusting for age, PSA, Gleason score, percentage of positive biopsy cores and clinical stage. The reported relative risks were 0.58 (95% CI 0.30−1.4, $p=0.11$) for unilateral nerve sparing and 0.64 (95% CI 0.35−1.17) for bilateral nerve sparing. Choi et al evaluated functional outcomes and positive margin rates in their series of 602 consecutive RARPs.[17] Nerve sparing improved 24-month urinary control without an increase in positive margin rates compared to nonnerve sparing RARP. Lastly, a study on the SEARCH (Shared Equal Access Regional Cancer Hospital) database including 1,018 cases echoed the previously stated findings, and reported that neither bilateral nor unilateral nerve sparing techniques were associated with a higher risk of a positive margin.[18]

Our findings are inconsistent with those reported in previous studies, for which we have two possible explanations. The potential confounders controlled for during analysis in previous studies were prostate specific and not prostate side specific. To determine causality between a nerve sparing approach and ipsilateral positive margins, each prostate lobe should be considered as a separate case. For example, it is likely that among patients in whom unilateral nerve sparing was performed the ipsilateral side had favorable tumor characteristics compared to the contralateral side. Disregarding the side specific factors in the analysis limits the ability to evaluate the causality between nerve sparing and an ipsilateral positive surgical margin and, therefore, the effects of side specific covariates remain masked.

The second reason regards the type and number of covariates adjusted for during multivariable analysis in previous studies. In this study the large sample size and side specific analysis enabled inclusion of a large number of potential confounders in the multivariable analysis, including the influence of the individual surgeon (and, thus, experience) on the occurrence of positive margins. To our knowledge, none of the previous studies performed an analysis including all of the most important potential predictors, including MRI stage, for positive margins.

In previously performed studies on this subject comparable conclusions were reported.[19,20] Zorn et al reported significantly higher posterolateral positive margin rates among patients with pT3 tumors who underwent interfascial nerve preservation compared to patients with pT3 tumors undergoing nonnerve sparing RARP (73% vs 33%, $p=0.05$).[20] That this study had comparable results may be explained by the methodological approach, as their analysis was also done on the lobe level. In addition, the nerve sparing technique performed was comparable to ours, as interfascial nerve sparing was performed.[19] Liss et al also reported nerve sparing to be associated with an increased risk of positive margins on multivariable analysis (OR 5.58, 95% CI 1.176-26.46).[19] However, the calculated ORs (and large corresponding 95% CIs) on multivariable analysis should be interpreted with caution as the number of events was relatively low (21) for the total number of covariates included (6).[18]

The positive margin rates, especially those observed for pT2 tumors (23%), were relatively high compared to those reported in other series. In a recent meta-analysis by Nguyen et al an absolute risk of positive margins of 8.1% for any nerve sparing and 7.7% for nonnerve sparing was reported.[7] The higher rates of positive margins observed in this study may be explained by the selection of higher risk patients for surgery, with highest biopsy Gleason score (65% Gleason 7 or higher) and relatively high pT3 rates (40%) compared to those reported in other series (42% Gleason 7 or higher and 19% pT3).[10] Surgeon experience was previously reported to be associated with positive margins after RARP, and could also explain the higher positive margin rates in our cohort.[21] Of all surgeons performing RARP in this study a large proportion were novice, with 8 of 14 (57%) having performed fewer than 50 RARPs.

Our study has a number of strengths, as it is a multicenter study with a large sample size, enabling inclusion of a relatively large number of covariates into the multivariable logistic regression model. However, some potential limitations must be

acknowledged. Our study lacks central review regarding histopathological findings on prostate biopsy and final pathology after RARP. However, we do not believe this has a large impact on our findings as positive surgical margin interpretation by uropathologists generally shows good agreement.[22] In addition, data regarding the degree of interfascial nerve sparing were lacking in the surgery reports, which could have led to measurement bias. Finally, inclusion of the location of positive surgical margins was outside the scope of the present study. Evaluation of the specific locations of the positive margins should be the subject of future research as the association between location and nerve sparing remains poorly understood.

CONCLUSION

Preservation of the neurovascular bundles during robot-assisted radical prostatectomy is associated with an increased risk of ipsilateral positive surgical margin when adjusting for patient and side specific covariates on multivariate analysis. The increased risk of ipsilateral positive margins should be taken into account when counseling patients who opt for nerve sparing RARP.

REFERENCES

1. Bill-Axelson A, Holmberg L, Garmo H et al: Radical prostatectomy or watchful waiting in prostate cancer—29-year follow-up. N Engl J Med 2018; **379:** 2319.
2. Mottet N, Bellmunt J, Bolla M et al: EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017; **71:** 618.
3. Johansson E, Steineck G, Holmberg L et al: Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. Lancet Oncol 2011; **12:** 891.
4. Donovan JL, Hamdy FC, Lane JA et al: Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2016; **375:** 1425.
5. Walsh PC and Donker PJ: Impotence following radical prostatectomy: insight into etiology and prevention. J Urol, suppl., 2017; **197:** S165.
6. Suardi N, Moschini M, Gallina A et al: Nerve-sparing approach during radical prostatectomy is strongly associated with the rate of post-operative urinary continence recovery. BJU Int 2013; **111:** 717.
7. Nguyen LN, Head L, Witiuk K et al: The risks and benefits of cavernous neurovascular bundle sparing during radical prostatectomy: a systematic review and meta-analysis. J Urol 2017; **198:** 760.
8. Chalfin HJ, Dinizo M, Trock BJ et al: Impact of surgical margin status on prostate-cancer-specific mortality. BJU Int 2012; **110:** 1684.
9. Preisser F, Mazzone E, Knipper S et al: Rates of positive surgical margins and their effect on cancer-specific mortality at radical prostatectomy for patients with clinically localized prostate cancer. Clin Genitourin Cancer 2019; **17:** e130.
10. Ficarra V, Novara G, Ahlering TE et al: Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol 2012; **62:** 418.
11. Epstein JI, Egevad L, Amin MB et al: The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016; **40:** 244.
12. Fine SW, Amin MB, Berney DM et al: A contemporary update on pathology reporting for prostate cancer: biopsy and radical prostatectomy specimens. Eur Urol 2012; **62:** 20.
13. Van Buuren S and Groothuis-Oudshoorn K: Multivariate imputation by chained equations in R. J Stat Soft 2011; **45:** 1.
14. RStudio Team: RStudio: Integrated development for R. Boston, Massachusetts: RStudio, Inc. 2015. Available at http://www.rstudio.com/.
15. Coelho RF, Chauhan S, Orvieto MA et al: Predictive factors for positive surgical margins and their locations after robot-assisted laparoscopic radical prostatectomy. Eur Urol 2010; **57:** 1022.
16. Moore BM, Savdie R, PeBenito RA et al: The impact of nerve sparing on incidence and location of positive surgical margins in radical prostatectomy. BJU Int 2012; **109:** 533.
17. Choi WW, Freire MP, Soukup JR et al: Nerve-sparing technique and urinary control after robot-assisted laparoscopic prostatectomy. World J Urol 2011; **29:** 21.
18. Nelles JL, Freedland SJ, Presti JC Jr et al: Impact of nerve sparing on surgical margins and biochemical recurrence: results from the SEARCH database. Prostate Cancer Prostatic Dis 2009; **12:** 172.
19. Liss M, Osann K and Ornstein D: Positive surgical margins during robotic radical prostatectomy: a contemporary analysis of risk factors. BJU Int 2008; **102:** 603.
20. Zorn KC, Gofrit ON, Orvieto MA et al: Robotic-assisted laparoscopic prostatectomy: functional and pathologic outcomes with interfascial nerve preservation. Eur Urol 2007; **51:** 755.
21. Bravi CA, Tin A, Vertosick E et al: The impact of experience on the risk of surgical margins and biochemical recurrence after robot-assisted radical prostatectomy: a learning curve study. J Urol 2019; **202:** 108.
22. Evans AJ, Henry PC, Van der Kwast TH et al: Interobserver variability between expert urologic pathologists for extraprostatic extension and surgical margin status in radical prostatectomy specimens. Am J Surg Pathol 2008; **32:** 1503.