Selection of patients for nerve sparing surgery in robot-assisted radical prostatectomy

André N. Vis1,2 | Roderick C. N. van den Bergh3 | Henk G. van der Poel2,4 | Alexander Mottrie5 | Philip D. Stricker6 | Marcus Graefen7 | Vipul Patel8 | Bernardo Rocco9 | Birgit Lissenberg-Witte10 | Pim J. van Leeuwen2,4

1Department of Urology, Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands
2Prostate Cancer Network, Netherlands
3Department of Urology, Antonius Hospital, Nieuwegein, The Netherlands
4Department of Urology, NKI/AVL, Amsterdam, The Netherlands
5Department of Urology, Onze Lieve Vrouw Hospital (OLV), Aalst, Belgium
6Department of Urology, St. Vincent’s Clinic, Sydney, NSW, Australia
7Martini-Klinik, University Hospital Hamburg-Eppendorf, Hamburg, Germany
8Global Robotics Institute, Florida Hospital Celebration Health, Orlando, Florida, USA
9Department of Urology, University of Modena and Reggio Emilia, Modena, Italy
10Department of Epidemiology and Data Science, Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands

Correspondence
André N. Vis, MD, PhD, Urologist, Associate Professor, Amsterdam University Medical Center, De Boelelaan 1117, Postbus 7057, 1007 MB Amsterdam, The Netherlands. Email: a.vis@amsterdamumc.nl

Abstract

Context: Robot-assisted radical prostatectomy (RARP) has become the standard surgical procedure for localized prostate-cancer (PCa). Nerve-sparing surgery (NSS) during RARP has been associated with improved erectile function and continence rates after surgery. However, it remains unclear what are the most appropriate indications for NSS.

Objective: The objective of this study is to systematically review the available parameters for selection of patients for NSS. The weight of different clinical variables, multiparametric magnetic-resonance-imaging (mpMRI) findings, and the impact of multiparametric-nomograms in the decision-making process on (side-specific) NSS were assessed.

Evidence acquisition: This systematic review searched relevant databases and included studies performed from January 2000 until December 2020 and recruited a total of 15,840 PCa patients. Studies were assessed that defined criteria for (side-specific) NSS and associated them with oncological safety and/or functional outcomes. Risk of bias assessment was performed.

Evidence synthesis: Nineteen articles were eligible for full-text review. NSS is primarily recommended in men with adequate erectile function, and with low-risk of extracapsular extension (ECE) on the side-of NSS. Separate clinical and radiological variables have low accuracy for predicting ECE, whereas nomograms optimize the risk-stratification and decision-making process to perform or to refrain from NSS when oncological safety (organ-confined disease, PSM rates) and functional outcomes (erectile function and continence rates) were assessed.

Conclusions: Consensus exists that patients who are at high risk of ECE should refrain from NSS. Several multiparametric preoperative nomograms were developed to predict ECE with increased accuracy compared with single clinical, pathological, or radiological variables, but controversy exists on risk thresholds and decision rules on a conservative versus a less-conservative surgical approach. An individual clinical judgment on the possibilities of NSS set against the risks of ECE is warranted.
Patient summary: NSS is aimed at sparing the nerves responsible for erection. NSS may lead to unfavorable tumor control if the risk of capsule penetration is high. Nomograms predicting extraprostatic tumor-growth are probably most helpful.

KEYWORDS
erectile dysfunction, evidence synthesis, nerve-sparing, prostate cancer, radical prostatectomy, systematic review

1 | INTRODUCTION

Robot-assisted radical prostatectomy (RARP) has shown excellent oncologic outcomes for men with localized prostate cancer (PCa) but carries a substantial risk of urinary incontinence and erectile dysfunction.1–4 A key determinant of functional outcome is the preservation of the neurovascular bundle (NVB) at the time of surgery. The NVB is a poorly defined anatomical structure that runs along the dorsolateral side of the prostate.5,6 It is functionally related to the autonomic nervous system and innervates the corpora cavernosa but has also been associated with the innervation of the external sphincter complex. Preserving the NVB in men undergoing RARP has been related to improved postoperative erectile function and improved urinary continence rates the first months after surgery compared with those not undergoing nerve-sparing surgery (NSS).1–8 A concern with NSS is that close surgical preparation along the prostatic capsule may inadvertently lead to a positive surgical margin (PSM) and potentially a noncurative resection. Several studies have documented the negative impact of PSM on biochemical recurrence after RARP.1,2,9 The risk of a PSM seems most present when extracapsular tumor extension (ECE) exists.10 Therefore, urological surgeons are reluctant to perform NSS close to the prostate when there is a concern and uncertainty about the local extent of the cancer, and this will lead to decreased postoperative functional recovery rates. Surgeons must plan NSS by balancing the competing functional and oncological outcomes. Therefore, it is optimally important to risk-stratify patients who opt RARP for (side-specific) NSS or otherwise for a non-NSS approach.

We performed a systematic review of the available literature in which (contra)indications for NSS in patients undergoing RARP were associated with oncological safety and/or functional outcomes. In this, the weight of different clinical variables, multiparametric-magnetic resonance imaging (mpMRI) parameters and of nomograms in the decision-making process on (side-specific) NSS were evaluated.

2 | EVIDENCE ACQUISITION

2.1 | Data acquisition and search strategy

A review was performed following the Preferred-Reporting Items for Systematic-Reviews and Meta-Analysis (PRISMA) statement (http://www.prisma-statement.org). The review protocol was published in the PROSPERO database.11 Both PubMed and Embase databases were searched for English language articles published from January 2000 until December 2020. Key Search terms included indexed terms (MeSh for PubMed; EMtree for EMBASE) as well as free-text terms. Terms expressing “prostatectomy” were used in combination with terms comprising “nerve-sparing.”

2.2 | Screening of abstracts and full-text articles

We first limited our search to abstracts of studies that may be used for inclusion. Full-text original articles were retrieved from the selected abstracts. Abstracts and original articles were independently assessed by two reviewers for eligibility (AV, PvL). Each citation was classified as inclusion, unsure, or exclusion. In case of disagreement, the manuscripts were discussed in a combined session. Agreement was obtained for all included papers. References of all full-text articles were screened to identify additional relevant articles not found in the PubMed, EMBASE, and MEDLINE databases. Secondary publications and (systematic) reviews on a similar subject or with part of the research question as a subject were omitted, as were abstracts without accompanying full-text articles. The final number of included and excluded studies (with the reason for exclusion) is reported in the PRISMA (Figure 1).

2.3 | Eligibility

As proposed by the PRISMA guidelines, we used the Population, Intervention, Comparator, Outcome, and Study (PICOS) design model to direct eligibility. The specific PICO is presented in Table 1. Studies were eligible if they included patients who opted for (robot-assisted) radical prostatectomy for histological proven PCAs and mentioned specific (contra)indications for (side-specific) NSS. As primary outcome, it was studied whether the proposed clinical and radiological variables for the (extent of) NSS were associated with oncological safety (organ-confined disease, rates of PSM) without compromising functional outcomes (erectile function and continence rates). Studies reporting on the prediction of ECE or extraprostatic extension (EPE) using preoperative variables only without a recommendation on NSS were excluded. Second, we looked for a change of surgical plan on NSS due to application of mpMRI.
After full-text evaluation, data from eligible studies were independently extracted by two reviewers. To avoid overlap of patient’s populations, if multiple publications reported on the same patient population, the largest study was included. The following data were independently extracted from full-text articles: number of patients, type of study, variables used to determine (side-specific) NSS, and the eventual proposed conditions to perform NSS, and oncological safety and functional outcomes (Table 2).

### 2.5 Risk of bias

Risk-of-bias (RoB) assessment was performed using the Cochrane recommendations for RoB assessment of nonrandomized controlled studies (NRS). It comprises the standard Cochrane domains and additionally includes assessment of five key prespecified confounding factors for NRSs. Potential subgroup analyses were preplanned based on the following variables: clinical tumor stage, initial prostate-specific antigen (PSA) level, biopsy Gleason score, other biopsy variables, features-on-MRI, nomograms, and algorithm. Two reviewers (AV, PVL) assessed RoB. Disagreement was resolved by discussion.

### 3 Evidence Synthesis

#### 3.1 Quantity of evidence identified

Our primary database search identified 1870 records, of which 54 full-text articles were screened for eligibility. Finally, 19 papers met the inclusion criteria for full-systematic review (Figure 1).
| Reference | Number of patients | Study design | Clinical and radiological parameters, and/or nomogram | Proposed (contra) indications for NSS | Outcome(s) |
|------------|--------------------|--------------|------------------------------------------------------|-------------------------------------|-------------|
| Graefen (2001) | N = 278, prospectively validated in 353 consecutive patients | Retrospective cohort study, prospectively validated | PSA, the number of biopsies with PCa, and with dominant Gleason grade 4 and 5 | Discrimination tool on (side specific) NSS based on: -Number of cores with Gleason grade 4/5 PCa (≤1, >1) -PSA (<10, ≥10) -Number of positive cores with PCa (≤1, >1) | The discrimination tool advises on (side specific) NSS for it correlates with organ-confined disease in the prostatectomy specimen |
| Shah (2003) | N = 272, new algorithm prospectively validated in 263 consecutive patients | Retrospective cohort study, prospectively validated | Biopsy Gleason score, percent tumor volume, perineural invasion | No NSS if (side specific): -Gleason score 6 and ≥50% biopsy tumor involvement and perineural invasion -Gleason score 7 and ≥30% biopsy tumor involvement and perineural invasion -Gleason score 8 and ≥10% biopsy tumor involvement and perineural invasion | Use of this NSS algorithm decreases PSM rates, while significantly increasing the preservation of neurovascular bundles |
| Hricak (2004) | N = 135 | Prospective cohort study | PSA, clinical tumor stage, biopsy Gleason score, tumor localization, percentage of positive for PCa biopsy cores, percentage of tumor involvement, MRI | Partin tables and risk of ECE were used to formulated extent of NSS from 1 (preserve) to 5 (completely resect) (not further specified) | Improved surgical planning such as on NSS with respect to organ-confined disease due to application of MRI |
| Kamat (2005) | N = 270 | Prospective cohort study | Biopsy Gleason score, length of tumor on biopsy core, location of biopsy cores with PCa | (Side specific) NSS is performed in: -Biopsy core with PCa <7 mm -Absence of core with PCa from the base of the prostate -Gleason score 8 or higher | Proposed criteria could assist in planning side specific NSS as EPE is often absent |
| Kessler (2007) | N = 536 | Retrospective cohort study | Clinical tumor stage, positive for PCa biopsy core, number of cores with PCa per side | NSS in nonpalpable disease, no biopsy core close to the NVB, maximum one core of PCa per side | Extent of NSS is associated with improved erectile function |
| Zorn (2008) | N = 155 | Retrospective cohort study | Clinical tumor stage, PSA, biopsy Gleason score, percentage of positive biopsy cores, maximal percentage of PCa on biopsy core | -Complete NSS: cT1c, PSA ≤6, Gleason score ≤6, <33% side-specific cores positive -Partial: cT2a, or cT1c with PSA >6, Gleason score 7, 33%–66% side-specific cores | A side-specific NSS protocol has reduced overall and pT2 rates of PSM. Erectile function data are not affected by nerve-sparing protocol |

(Continues)
| Reference       | Number of patients | Study design          | Clinical and radiological parameters, and/or nomogram | Proposed (contra) indications for NSS | Outcome(s)                                                                 |
|-----------------|--------------------|-----------------------|-------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------------|
| Hashimoto (2010) | N = 82             | Retrospective cohort study | PSA, clinical tumor stage, biopsy core positive for PCA in the apex, Gleason score | Algorithm on NSS using: -DRE (T1c, T2a, T2b vs. T2c) -Biopsy core in the apex (negative, positive) -PSA (<10 vs. ≥10) -Gleason score (6 vs. ≥7) | NSS caused NVB preservation without affecting PSM                         |
| McClure (2012)  | N = 105            | Retrospective cohort study | PSA, clinical tumor stage, biopsy Gleason score, number of cores with PCA, percentage of positive cores with PCA, tumor length, features on MRI | NSS was performed in those with low risk of ECE (not specified) with and without mpMRI findings | Data on MRI may improve the surgical plan to preserve or resect the NVB without compromising PSM rates |
| Srivastana (2013)| N = 1417           | Retrospective cohort study | PSA, clinical tumor stage, biopsy Gleason score, MRI, intraoperative visual cues | 4 risk grades of NSS based on: -PSA (<4, 4 – 10, 10-20, <20) -Clinical stage (T1, T2a-T2b, T2c, T3) -Gleason score (6, 3 + 4, 4 + 3, ≥8) and features on MRI (negative, visible, micro EPE, gross EPE) -Visual cues intraoperatively | Grade of NSS was associated with early return of continence               |
| Park (2014)     | N = 353            | Retrospective cohort study | Clinical tumor stage, PSA, biopsy Gleason score, MRI | A combination of variables such as palpable tumor or not, PSA <10 and ≥10, Gleason score (<7 and ≥7), unknown assessment, with and without MRI | Data on MRI may improve the surgical plan to preserve or resect the NVB without compromising oncological outcome |
| Kumar (2017)    | N = 557, high-risk PCA | Retrospective cohort study | Clinical tumor stage, positive for PCA cores, intraoperative visual cues | -Complete NSS: nonpalpable, <3 cores with PCA -Partial: non-palpable, <4 cores with PCA -None: Palpable, ≥4 cores involvement -Including visual cues | Selective NSS provides for reasonable intermediate term oncological and functional outcomes |
| Patel (2017)    | N = 6360           | Retrospective cohort study | Age, PSA, clinical tumor stage, rate of positive cores, rate | A decision rule on NSS based on the extent of ECE using 7 | Depending on the expected extent of ECE using the |

(Continues)
| Reference       | Number of patients | Study design       | Clinical and radiological parameters, and/or nomogram                                                                 | Proposed (contra) indications for NSS                                                                 | Outcome(s)                                                                 |
|-----------------|-------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Nyarangi-Dix (2018) | N = 264           | Retrospective cohort study | Clinical tumor stage, PSA, ISUP grade, and MRI variables (ESUR classification for EPE, MRI volume, capsule contact length) | Nomogram for the prediction of (side specific) ECE using clinical, biopsy and radiological variables. | A predictive nomogram for ECE was developed.                                  |
| Schiavina (2018) | N = 137           | Retrospective cohort study | PSA, clinical tumor stage, biopsy Gleason score, number and location of positive PCa cores, MRI                        | A combination of variables (not further specified), with and without MRI findings                      | mpMRI improves the oncological safety of NSS and reduces PSM               |
| Martini (2018)   | N = 561           | Retrospective cohort study | PSA, biopsy Gleason grade group, maximum percentage of tumor in the biopsy core with the highest Gleason score, ECE on mpMRI | Nomogram for the prediction of ECE using clinical, biopsy and radiological variables. The number of PSM that occur above a 10%, 15%, and 20% threshold | A predictive nomogram for ECE was developed. Using a 20% threshold, the rate of PSM is reduced |
| Alessi (2019)    | N = 308           | Retrospective cohort study | PSA, biopsy Gleason score, clinical tumor stage (EAU risk group), PI-RADS on MRI, ESUR-EPE score                        | Nomogram for the prediction of ECE using clinical, biopsy and radiological variables. Cut-off levels for (side specific) NSS are not specified | The predictive nomogram could assist in (side specific) NSS in those with low risk of ECE |
| Jäderling (2019) | N = 1031          | Retrospective cohort study | PSA, biopsy Gleason score, length of tumor on biopsy core, clinical tumor stage                                      | Intrafascial, interfascial or extrafascial NSS (not specified) with and without mpMRI                  | Application of MRI results in more bilateral non-NSS and results in a lower rate of PSM |
| Song (2020)      | N = 314, low-intermediate risk | Retrospective cohort study | Age, PSA, PSA-density, free-to-total PSA, prostate volume, clinical tumor stage, Gleason score, PI-RADS classification on mpMRI | Multivariate logistic regression analysis using clinical, biopsy and radiological variables           | A predictive model using PI-RADS, PSA-density, and biopsy Gleason score was developed and could assist in (side specific) NSS |
| Soeterik (2020)  | N = 625           | Retrospective cohort study | PSA, ISUP-grade, percent highest biopsy tumor involvement, EPE on MRI,                                               | Nomogram for the prediction of (side specific) ECE using clinical, biopsy and radiological variables.  | A risk assessment based on this nomogram is not recommended due to poor performance. Preservation of the NVB is associated with an increased |
TABLE 2 (Continued)

| Reference | Number of patients | Study design | Clinical and radiological parameters, and/or nomogram | Proposed (contra) indications for NSS | Outcome(s) |
|-----------|--------------------|--------------|------------------------------------------------------|--------------------------------------|------------|
|           |                    |              | specific, though leads to overtreatment non-NSS when adjusting for patient and side specific covariates | | risk of ipsilateral positive surgical margin. |

Abbreviations: AUC, area under the curve; ECE, extracapsular extension; EPE, extraprostatic extension; ESUR, European Society of Uroradiology; ISUP, International Society of Uropathology; mpMRI, multiparametric magnetic resonance imaging; N/A, not applicable; NSS, nerve-sparing surgery; NVB, neurovascular bundle; PI-RADS, Prostate Imaging Reporting and Data System, in 1–5; PCa, prostate cancer; PSA, prostate-specific antigen, in ng/ml; PSM, positive surgical margin.

3.2 | Characteristics of selected-studies

A total of 15 840 patients were included in this review. Most eligible studies were retrospective observational cohort studies in design. Three cohort studies determined the extent of NSS on a prospective basis, based on patients’ clinical and radiological variables. No randomized clinical trials (RCTs) were identified in our search process.

Nine studies assessed separate clinical, biochemical, and pathological variables to assist in recommendations on NSS,15–21,25,26 whereas six studies added MRI findings to their models22–24,28,31,32 (Table 2). Four studies developed a multiparametric nomogram.27,29,30,33 Seven studies associated recommendations on NSS with organ-confinement of disease,15–18,26,27,30,32 10 with positive surgical margin or oncological outcome,16,20–22,24,25,28–30,33 and four with functional outcomes18,19,23,25 (Table 2).

3.3 | RoB and confounding assessment of the included studies

The RoB assessment of all included studies are presented in Figure 2. RoB and confounding factors were assessed for each study individually. There was high RoB for selection, performance, detection, attrition, and reporting bias, due to the lack of RCTs. Only a few studies had low to moderate confounding bias for clinical tumor stage, initial PSA, biopsy Gleason score, other biopsy variables, (mp)MRI, and nomograms/algorithms, whereas others did not report or corrected for these variables.

4 | RESULTS OF EVIDENCE SYNTHESIS

4.1 | Prediction models of clinical variables, mpMRI and nomograms to assist in NSS (Table 2)

Numerous papers have addressed the preoperative prediction of ECE mostly using clinical parameters and some with the addition of mpMRI, but do not specifically recommend on surgical technique or NSS.34 In the past, side-specific NSS was advised only to patients with well-differentiated PCa without a positive biopsy core at the ipsilateral side.25,34 Thereafter, NSS was based on the number of ipsilateral positive cancer biopsy cores and biopsy Gleason score.16,18,19,37,38 Graefen et al. were one of the first to develop an easy-to-use, objective, and reproducible discriminative tool to select patients for side-specific NSS based on PSA and the number of cores with cancer and high-grade cancer.38 Moreover, they showed for the first time that multivariate risk-prediction based on multiple clinical variables improved the accuracy of patient selection for NSS. Since this study was published in 2001, mpMRI was not yet applied. Similarly, Zorn et al. developed a tailored-approach on NSS based on clinical stage, biopsy Gleason score, percentage of ipsilateral cores positive for cancer, and the maximum percentage of cancer involvement.20 Song et al. studied 639 patients who underwent preoperative mpMRI followed by radical prostatectomy for clinically localized PCa. Based on the Prostate Imaging Reporting and Data System (PI-RADS) of mpMRI, PSA density and biopsy Gleason score, a model was constructed that could help in the selection of suitable candidates for NSS.32 In line with previous works, the predictive value of these multivariate models was better than any single risk factor. Similarly, Alessi et al. made a nomogram using the European Association of Urology (EAU) classification risk group, the European Society of Uroradiology (ESUR) EPE score for any lesion in contact with the prostate capsule and the PI-RADS score for the prediction of ECE and higher in the radical prostatectomy specimen.30 The nomogram was used to advise on NSS, although an area under the curve (AUC) optimum to perform NSS was not provided. Martini et al. developed a guide for nerve-sparing RARP based on a model including 589 patients for the prediction of side-specific ECE. Predictors in this model were PSA, highest Gleason score in the prostatic lobe, maximum percentage of cores from the highest Gleason-grade and documented T3 on mpMRI.29 The performance of the multivariate model was good (AUC 82.9%) and significantly better compared with mpMRI alone (AUC 68.8%). Interestingly, they described the number of ECE cases (and corresponding PSMs) that occurred above the 10%, 15%, and 20% threshold. Using a 20% threshold, a majority of PSM could be avoided by performing non-NSS. An external validation of the nomogram was...
performed with moderate-to low discriminative capability. Soeterik et al. further updated the nomogram of Martini and with a risk-threshold set at 20% were able to safely perform side-specific NSS in the majority of patients. Nyarangi-Dix et al. developed a nomogram in 264 surgically treated patients which was largely based on Gleason grade, preoperative MRI-findings including prostate volume, ESUR-classification for EPE, and tumor capsular contact length. Despite performing well, it was not validated externally. From a Japanese study group, a simple decision-making algorithm on NSS was developed using clinical tumor stage (T1c-T2b vs. T2c), PSA (≥10 ng/ml vs. <10 ng/ml) and apical biopsy Gleason score (≥7 vs. <7). Despite easy-to-use, the algorithm was not prospectively evaluated.

Srivastana et al. from the group of Ash Tewari proposed a risk-stratified grade of (side-specific) NSS in which PSA, clinical tumor stage, biopsy Gleason score, and findings on mpMRI determined the extent of NSS along with visual cues intraoperatively. Although a large number of patients was studied, this study was retrospective in design, with the grade of NSS being a subjective measure and not being standardized.

4.2 | Change of surgical plan on NSS due to application of mpMRI

One of the earlier studies evaluating MRI on surgical plan evaluated 144 patients undergoing radical prostatectomy. This study group showed that when a preoperative probability of <25% of organ-confined disease was assessed using the Partin-staging tables, MRI changed the surgical plan in 78% of patients and favored NSS in 83% of patients. MRI had shown to have an incremental value in the clinical assessment additive to currently applied nomograms, although in this series functional-imaging by dynamic contract enhanced (DCE) imaging and diffusion weighted imaging (DWI) was not applied. Using the same criteria as Martini et al. for the extent of NSS, Schiavina et al. studied two cohorts of patients and determined whether mpMRI changed the surgical plan on NSS. Indeed, mpMRI changed surgical plans equally between the direction of more radical and a less radical approach. Unfortunately, it was not clear based on what features the extent of surgery was chosen. Jägerling et al. found in their series of 1037 surgically treated patients that mpMRI was associated with
an increased chance of undergoing bilateral non-NSS versus any type of NSS (RR1.84 [95% CI 1.11–3.03]). There was a slightly increased chance of undergoing bilateral NSS in those who did not undergo mpMRI (RR1.09 [95% CI 1.00–1.20]) compared with unilateral or non-NSS.21

Park et al. studied 353 men who underwent radical prostatectomy with a preoperative mpMRI where the surgeon determined preoperatively the degree of NSS based on PSA level, that is, NSS in those with PSA < 10 ng/ml, nonpalpable tumors and a biopsy Gleason score below 7. They determined NSS without incorporating mpMRI findings and then once again after reviewing the mpMRI. The surgical plan was changed in 26% of the patients, to either a more aggressive NSS approach (57%) or a wider margin of resection (43%). In patients with intermediate and high-risk features, a change of surgical plan was made more often after reviewing the mpMRI, that is, in 31% and 40% of cases, respectively.24 Similarly, McClure et al. showed that the initial surgical plan was changed in 28 of 104 (27%) patients after reviewing the MRI.22 The surgical plan was changed to NSS in 17 out of 28 patients (61%) and to a non-NSS in 11 (39%). In patients whose surgical plan was changed to NSS, there were no PSM on the side of the prostate with a change in treatment plan.

5 | DISCUSSION

RARP is the main curative surgical approach in men with localized PCa. Despite providing a high chance of cancer control, RARP is associated with a nonnegligible risk of erectile dysfunction and urinary incontinence.1,2 These downsides of RARP may have a detrimental impact on a patients’ health-related quality of life (HRQoL) during follow-up.41–43 Advances in surgical technique and understanding of the pelvic floor anatomy have allowed for the preservation of the NVB, which have repeatedly been shown to improve functional outcomes after surgery.1–7 NSS is particularly aimed to preserve these bundles and to prevent the negative sequelae of RARP and maintain HRQoL after surgery. We performed a systematic review to investigate the indications for NSS in RARP and to study the use of various clinical variables and mpMRI and of nomograms in the decision-making process on (side-specific) NSS.

Most currently applied PCA guidelines recommend NSS primarily in younger men with adequate erectile function.44–48 Different meta-analyses demonstrated that patients undergoing NSS had improved continence rates in the first months after RARP, but the studies come to different conclusions for the period after 6 months.1–5 It has been argued, however, that even early improvement in urinary continence (<3 months after surgery) is enough to perform NSS with respect to the improvement in HRQoL.49 Therefore, NSS might be performed regardless of potency status.50 Despite these recommendations, few studies have addressed age and preoperative functions into their predictive models.

In the PCA guidelines of the EAU and American Urological Association (AUA), it is advocated that NSS should be offered to patients with localized PCA undergoing RARP.44,45 The concept of locally confined versus locally advanced disease, however, is poorly defined. Commonsensically, one should refrain from NSS in the presence of a tumor that extends through the prostate capsule and grows into the NVB. Sparing the NVB would inevitably lead to a PSM and thereby to biochemical and/or local recurrence of disease.10,50 As such, the selection for NSS comes down to accurate local tumor staging and the ability to define the precise tumor’s anatomy.

Historically, tumor staging relied heavily on digital rectal examination (DRE), transrectal ultrasound (TRUS) imaging, and the biopsy Gleason score. Unfortunately, preoperative clinical staging based on DRE and biopsy as separate variables has limited accuracy with under staging of locally extensive disease in a substantial number of cases.51,52 Clinical variables were often combined into algorithms such as the Partin tables and the Ohori, Steuber, Briganti, and Memorial Sloan Kettering Cancer Center (MSKCC) nomograms.53–58 The advent of novel imaging tools, particularly mpMRI, was believed to improve clinical staging and to assist in proper surgical planning such as resection of the NVB or NSS.59–60 However, in a recent meta-analysis involving 9796 patients from 75 different studies, the sensitivity of mpMRI for ECE reached 0.57 only (95% CI 0.49–0.64), with a specificity of 0.91 (95% CI 0.88–0.93).61 This implies that ECE is present in a substantial proportion of patients who showed no signs of capsule penetration on mpMRI. Consequently, the sensitivity of mpMRI as a single variable seems inadequate to safely exclude the presence of T3 tumors and to perform NSS accordingly.52

The use of nomograms is recommended by different PCA guidelines to improve preoperative risk assessment of ECE.44–46 Nomograms allow to make complex risk estimations, outperforming individual clinical parameters. The above-mentioned probability nomograms considered PSA, clinical tumor stage, and biopsy Gleason score, but not mpMRI. Adding mpMRI to these models has further improved the predictive accuracy for ECE.62 Indeed, several retrospective studies used either serum PSA, biopsy Gleason score, other prostate biopsy variables, and PI-RADS score on mpMRI to predict organ-confined disease. So, the predictive capability of multivariate prediction models instead of single parameters such as (side-specific) biopsy Gleason score or mpMRI has the best predictive performance for non-organ-confined disease and may guide surgeons into proper decision making on NSS. However, from most of these studies, we were unable to find clear risk thresholds that may help clinicians in their decision to perform or to refrain from NSS. In a theoretical proposal, Lepor et al. were one of the few who made recommendations on specific thresholds to perform or to refrain from NSS. By applying a calculation using the location of ECE and the risk of PSM in ECE, cases with a ≥30% risk of ECE should be withheld NSS.64 A (side-specific) threshold of 20% under which NSS could be safely performed was proposed using nomograms incorporating both clinical parameters and readily applicable mpMRI variables.33,40 This threshold may be altered based on patients’ (oncological) objectives, age, and baseline erectile function.

Recent recommendations suggest that the extent of ECE may determine the approach to and the extent of NSS. Dissections performed closer to the prostate (e.g., extrafascial, interfascial, and
intrafascial) and bilaterally instead of unilaterally associated with superior functional outcomes. Patel et al. developed a decision rule to assist surgeons in their decision-making process on NSS based on the extent of ECE. Based on 6360 surgically treated patients, a predictive algorithm of the (side-specific) width of ECE (in mm) was constructed providing a suggestion to the surgeon regarding the boundaries of the resection. Unfortunately, a clear association of the graded approach to NSS with functional outcomes was not reported. NSS in patients with high-risk features (i.e., Gleason grade \( \geq 4 \) or \( \geq T2 \)) was often discouraged as the risk of ECE and PSM is increased. Kumar et al., however, indicated in a retrospective study that selective partial or complete NSS was still feasible in a series of high-risk patients with PCa with oncological outcomes that proved similar to those who underwent non-NSS.

It is important to state that in a systematic review and meta-analysis including 124 studies with 73,448 patients, NSS did not increase PSM rates, nor did it compromise cancer control if patients were carefully selected depending on tumor location, size, and grade. However, in a large multicenter study including 2574 patients, Soeterik et al. showed that NSS was associated with an increased risk of PSM when side-specific PSM was concerned. So, in patients with a specific wish to maintain erections, adequate counseling on the possibility of partial and unilateral/bilateral NSS and on functional recovery and oncological outcome after NSS is mandatory.

Despite the finding that existing nomograms may help urological surgeons to plan on NSS, a significant proportion of NSS techniques during RARP are changed intraoperatively. Reasons for deviation in technique can include challenging anatomical features (e.g., narrow pelvis and fatty tissues), disrupted surgical planes due to previous treatments or sepsis, and other factors leading to more difficult resections. Couture et al. showed that 46.9% of surgically treated cases had a change of surgical plan intraoperatively, in which increasing age was shown to be the most significant variable responsible for a change of management. The authors stated that surgeons are less likely to perform NSS in older patients in whom surgical planes are difficult to locate. Other variables associated with a higher rate of conversion of surgical plan were postbiopsy sepsis, high unilateral biopsy Gleason score, and larger prostates. Interestingly, the number of lifetime biopsies was not a significant predictor of unplanned non-NSS, a particularly novel and valuable finding for patients under active surveillance.

Furthermore, only few of the decision-making tools for EPE have been externally validated within 5 years after development and often perform poor. Adding mpMRI-findings may potentially improve the predictive performance of these nomograms. Though, urological surgeons need to consider the limitations of these decision tools when applying them on their own patients.

The efficacy and safety of perioperative Neurovascular Structure Adjacent Frozen Section Examination (NeuroSAFE) is being investigated in RCTs. Nonrandomized studies have shown that NeuroSAFE is able to improve NSS rates while it may help to achieve a modest reduction in PSM rates. Functional outcomes and long-term oncological outcomes need to be further explored. However, the establishment of the respective infrastructure to routinely perform the NeuroSAFE investigation intraoperatively is labor intensive and not possible in every institution. Furthermore, the feasibility of 3D imaging techniques and augmented-reality using preoperative mpMRI incorporated into the robotic systems and/or the use of 3D reconstructions and 3D prints of the prostate is investigated and could possibly assist the surgeon into making a proper surgical plan on the side and extent of NSS. At last, implementing modern PSMA-PET imaging into predictive nomograms, according to the newly developed e-PSMA guidelines, may be used to predict the side of ECE, increase the rate of (side-specific) NSS, lower PSM rates, and improve functional outcomes even in non-organ-confined disease.

This review was performed robustly in accordance with recognized standards, with a broad search strategy designed by a statistician/bio-epidemiologist. Limitations include the retrospective, single-institution nature of the majority of included studies. The absence of RCTs and the overall significant clinical and methodological risk of bias across studies make the quality of the evidence inherently low.

6 | CONCLUSIONS

Current literature suggests that NSS should not be performed in patients with a high likelihood of (extensive) ECE. At present, the use of preoperative multiparametric nomograms including mpMRI is suggested, and these nomograms are applied with improved diagnostic accuracy than single clinical, pathological, or radiological variables. Controversy exists on risk thresholds and on decision rules for a conservative versus a less conservative surgical approach of NSS. Individual clinical judgment may still consider the patient’s specific wish to maintain erections and the patient’s consent for potentially discounting cure.

ACKNOWLEDGEMENT

None.

AUTHOR CONTRIBUTION

A.N. Vis: Design, writing and statistical analysis. R.C. van den Berg: Design, writing and supervision. H. van der Poel: Writing and review. A. Mottrie: Writing and review. V. Patel: Writing and review. P. Stricker: Writing and review. M. Graefen: Writing and review. B. Rocco: Writing and review. B. Lissenberg-Witte: Statistical review. P. van Leeuwen: Design, writing, statistical analysis, supervision.

ORCID

André N. Vis https://orcid.org/0000-0003-3419-3368
Henk G. van der Poel https://orcid.org/0000-0002-8772-1120
Alexander Mottrie https://orcid.org/0000-0002-1253-1592
Philip D. Stricker https://orcid.org/0000-0002-0934-0656
Marcus Graefen https://orcid.org/0000-0003-3609-3512
Bernardo Rocco https://orcid.org/0000-0002-9135-0035
REFERENCES

1. 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;62:418–30. https://doi.org/10.1016/j.euro.2012.05.045

2. Ficarra V, Novara G, Rosen RC, Artibani W, Carroll PR, Costello A, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol. 2012;62:405–17. https://doi.org/10.1016/j.euro.2012.05.045

3. Reeves F, Preece P, Kapoor J, Everaerts W, Murphy DG, Corcoran NM, et al. Preservation of the neurovascular bundles is associated with improved time to continence after radical prostatectomy but not long-term continence rates: Results of a systematic review and meta-analysis. Eur Urol. 2015;68:692–704. https://doi.org/10.1016/j.euro.2014.10.020

4. Nguyen LN, Head L, Wüthik K, Punjani N, Mallick R, Crossen S, et al. The risks and benefits of cavernous neurovascular bundle sparing during radical prostatectomy: A systematic review and meta-analysis. J Urol. 2017;198:760–9. https://doi.org/10.1016/j.juro.2017.02.3344

5. Panebianco V, Barchetti F, Sciarra A, Marcantonio A, Zini C, Salciccia S, et al. In vivo 3D neuroanatomical evaluation of periprostatic nerve plexus with 3T–MR diffusion tensor imaging. Eur J Radiol. 2013;82:1677–82. https://doi.org/10.1016/j.ejrad.2013.05.013

6. Alsaid B, Karam I, Bessede T, Abdlsamad I, Uhl JF, Delmas V, et al. Tridimensional computer-assisted anatomic dissection of posterolateral prostate neurovascular bundles. Eur Urol. 2010;58:281–7. https://doi.org/10.1016/j.ejuro.2010.04.002

7. Walsh PC, Mostwin JL. Radical prostatectomy and cystoprostatectomy with preservation of potency. Results using a new nerve-sparing technique. Br J Urol. 1984;56:694–7. https://doi.org/10.1111/j.1464-410x.1984.tb06149.x

8. Vis AN, van der Poel HG, Ruiter AEC, Hu JC, Tewari AK, Rocco B, et al. Posterior, anterior, and periurethral surgical reconstruction of urinary continence mechanisms in robot-assisted radical prostatectomy: A description and video compilation of commonly performed surgical techniques. Eur Urol. 2019;76:814–22. https://doi.org/10.1016/j.eururo.2018.11.035

9. Rajan P, Hagman A, Sooriakumaran P, Nyberg T, Wallerstedt A, Addings C, et al. Oncologic outcomes after robot-assisted radical prostatectomy: A large European single-Centre cohort with median 10-year follow-up. Eur Urol Focus. 2018;4:351–9. https://doi.org/10.1016/j.euf.2016.10.007

10. Yossepowitch O, Briganti A, Eastham JA, Epstein J, Graefen M, Montironi R, et al. Positive surgical margins after radical prostatectomy: A systematic review and contemporary update. Eur Urol. 2014;65:303–13. https://doi.org/10.1016/j.eururo.2013.07.039

11. http://www.crd.york.ac.uk/PROSPERO; registration number CRD42018088063.

12. EAU Handbook for Guidelines Development. 2017.

13. Dow JN, Sylvester R, Knoll T, Lam T, Canfield S, Plass K, et al. EAU Guidelines Systematic Reviews Methods and Processes Handbook 2016:1–29

14. Knoll T, Omar MI, MacIennan S, Hernández V, Canfield S, Yuan Y, et al. Key steps in conducting systematic reviews for underpinning clinical practice guidelines: Methodology of the European Association of Urology. Eur Urol. 2018;73:290–300. https://doi.org/10.1016/j.euro.2017.08.016

15. Graeven M, Haese A, Pichlemeier U, Hammerger PG, Noldus J, Butz K, et al. A validated strategy for side specific prediction of organ confined prostate cancer: A tool to select for nerve sparing radical prostatectomy. J Urol. 2001;165:857–63.

16. Shah O, Robbins DA, Melamed J, Lepor H. The new York University nerve sparing algorithm decreases the rate of positive surgical margins following radical retropubic prostatectomy. J Urol. 2003;169:2147–52. https://doi.org/10.1016/j.juro.2003.07.046

17. Hricak H, Wang L, Wei DC, Coakley FV, Akin O, Reuter VE, et al. The role of preoperative endorectal magnetic resonance imaging in the decision regarding whether to preserve or resect neurovascular bundles during radical retropubic prostatectomy. Cancer. 2004;100:2655–63. https://doi.org/10.1002/cncr.20319

18. Kamat AM, Jacobsohn KM, Troncoso P, Shen Y, Wen S, Babaian RJ. Validation of criteria used to predict extraprostatic cancer extension: A tool for use in selecting patients for nerve sparing radical prostatectomy. J Urol. 2005;174:1262–5. https://doi.org/10.1097/01.ju.0000173914.26476.7c

19. Kessler TM, Burkhard FC, Studer UE. Nerve-sparing open radical retropubic prostatectomy. Eur Urol. 2007;51:90–7. https://doi.org/10.1016/j.euro.2006.10.013

20. Zom KC, Gofrit ON, Steinberg GP, Taxy JB, Zajagà GP, Shalhav AL. Planned nerve preservation to reduce positive surgical margins during robot-assisted laparoscopic radical prostatectomy. J Endourol. 2008;22:1303–9. https://doi.org/10.1089/end.2008.0009

21. Hashimoto K, Hisasue S, Masumori N, Kobayashi K, Kato R, Fukuta F, et al. Clinical safety and feasibility of a newly developed, simple algorithm for decision-making on neurovascular bundle preservation in radical prostatectomy. Jjco. 2010;40:343–8. https://doi.org/10.1093/jjco/hyp157

22. McClure TD, Margolis DJ, Reiter RE, Sayre JW, Albert M, Thomas MA, et al. Use of MR imaging to determine preservation of the neurovascular bundles at robotic-assisted laparoscopic prostatectomy. Radiology. 2012;262:874–83. https://doi.org/10.1148/ radiology.11103504

23. Srivastava A, Chopra S, Pham A, Sooriakumaran P, Durand M, Chughtai B, et al. Effect of a risk-stratified grade of nerve-sparing technique on early return of continence after robot-assisted laparoscopic radical prostatectomy. Eur Urol. 2013;63:438–44. https://doi.org/10.1016/j.eururo.2012.07.009

24. Park BH, Jeon HG, Jeong BC, Seo SI, Lee HM, Choi HY, et al. Influence of magnetic resonance imaging in the decision to preserve or resect neurovascular bundles at robotic assisted laparoscopic radical prostatectomy. J Urol. 2014;192:828–8. https://doi.org/10.1016/j.juro.2014.01.005

25. Kumar A, Samavedi S, Bates AS, Mouraviev V, Coelho RF, Rocco B, et al. Safety of selective nerve sparing in high risk prostate cancer during robot-assisted radical prostatectomy. J Robot Surg. 2017;11:373–82. https://doi.org/10.1007/s11701-016-0627-3

26. Patel VR, Sandri M, Grasso AAC, Lorenzis E, Palmisano F, Albo G, et al. A novel tool for predicting extracapsular extension during graded partial nerve sparing in radical prostatectomy. BJU Int. 2018;121:373–82. https://doi.org/10.1111/bju.14026

27. Nyarangi-Dix J, Wiesenfarth M, Bonekamp D, Hittthaler B, Schütz V, Dieffenbacher S, et al. Combined clinical parameters and multi-parametric magnetic resonance imaging for the prediction of extra-prostatic disease—A risk model for patient-tailored risk stratification when planning radical prostatectomy. Eur Urol Focus. 2018;23:1205–12. https://doi.org/10.1016/j.euf.2018.11.004

28. Schiavina R, Bianchi L, Borghesi M, Dababneh H, Chessa F, Pultrone CV, et al. MRI displays the prostatic cancer anatomy and improves the bundles management before robot-assisted radical prostatectomy. J Endourol. 2018;32:315–21. https://doi.org/10.1089/end.2017.0701
29. Martini A, Gupta A, Lewis SC, Cumarsamy S, Haines KG 3rd, Brigantni A, et al. Development and internal validation of a side-specific, multiparametric magnetic resonance imaging-based nomogram for the prediction of extracapsular extension of prostate cancer. BJU Int. 2018;122:1025–33. https://doi.org/10.1111/j.bju.14353

30. Alessi S, Piccolo P, Summers P, Femina M, Tagliabue E, Renne G, et al. Low PI-RADS assessment category excludes extraprostatic extension (≥pT3a) of prostate cancer: A histological-validated study including 301 operated patients. Eur Radiol. 2019;29:5478–87. https://doi.org/10.1007/s00330-019-06092-0

31. Jäderling F, Akre O, Aly M, Björklund J, Olsson M, Adding C, et al. Preoperative staging using magnetic resonance imaging and risk of positive surgical margins after prostate-cancer surgery. Prostate Cancer Prostatic Dis. 2019;22:391–8. https://doi.org/10.1038/s41391-018-0116-z

32. Song G, Ruan M, Wang H, Lin Z, Wang X, Li X, et al. Predictive model using prostate MRI findings can predict candidates for nerve sparing radical prostatectomy among low-intermediate risk prostate cancer patients. Transl Androl Urol. 2020;9:437–44. https://doi.org/10.21037/tau.2020.01.28

33. Soeterik TFW, van Melick HHE, Dijksman LM, Küsters-Vandevelde HVN, Biesma DH, Witjes JA, et al. External validation of the Martini nomogram for prediction of side-specific extraprostatic extension of prostate cancer in patients undergoing robot-assisted radical prostatectomy. Urol Oncol. 2020;38:372–8. https://doi.org/10.1016/j.juroncol.2019.12.028

34. Rocco B, Sighinolfi MC, Sandri M, Eissa A, Elsherbyny A, Zoir A, et al. Is extraprostatic extension of cancer predictable? A review of predictive tools and an external validation based on a large and single center cohort of prostate cancer patients. Urology. 2019;129:8–20. https://doi.org/10.1016/j.jurology.2019.03.019

35. Walsh PC. Radical prostatectomy, preservation of sexual function, cancer control. Controversy Urol Clin North Am. 1987;14:663–73.

36. Catalona WJ. Patient selection for, results of, and impact on tumor regression of potency-sparing radical prostatectomy. Urol Clin North Am. 1990;17:819–26.

37. Sanwick JM, Dalkin BL, Nagle RB. Accuracy of prostate needle biopsy in predicting extracapsular tumor extension at radical retropubic prostatectomy: Application in selecting patients for nerve-sparing urology. Urol. 1998:52:814–8. https://doi.org/10.1016/s0090-4295(98)00399-9

38. Graefen M, Hammerer P, Michl U, Noldus J, Haese A, Henke RP, et al. Incidence of positive surgical margins after biopsy-selected nerve-sparing radical prostatectomy. Urol. 1998;51:437–42. https://doi.org/10.1016/s0090-4295(97)00608-0

39. Sighinolfi MC, Sandri M, Torricelli P, Ligabue G, Fiocchi F, Scialpi M, et al. External validation of a novel side-specific, multiparametric magnetic resonance imaging-based nomogram for the prediction of extracapsular extension of prostate cancer: Preliminary outcomes on a series diagnosed with multiparametric magnetic resonance imaging-targeted plus systematic saturation biopsy. BJU Int. 2019;124:192–4. https://doi.org/10.1111/bju.14665

40. Soeterik TFW, van Melick HHE, Dijksman LM, Stomps S, Witjes JA, van Besten JPA. Nerve sparing during robot-assisted radical prostatectomy increases the risk of ipsilateral positive surgical margins. J Urol. 2020;204:91–5. https://doi.org/10.1097/JU.0000000000000760

41. Johansson E, Steineck G, Holmberg L, Johansson JE, Nyberg T, Ruutu M, 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;12:891–9. https://doi.org/10.1016/s1470-2045(11)70162-0

42. Donovan JL, Handy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med. 2016 Oct 13;375(15):1425–37. https://doi.org/10.1056/NEJMoa1606221

43. King MT, Viney R, Smith DP, Hossain I, Street D, Savage E, et al. Survival gains needed to offset persistent adverse treatment effects in localised prostate cancer. Br J Cancer. 2012;106:638–45. https://doi.org/10.1038/bjc.2011.552

44. https://uroweb.org/guideline/prostate-cancer/?type=panel

45. https://www.auanet.org/guidelines/prostate-cancer-clinically-localized-guideline

46. https://www.esmo.org/guidelines/genitourinary-cancers/prostate-cancer

47. Michl U, Tennstedt P, Feldmeier L, et al. Nerve-sparing surgery technique, not the preservation of the neurovascular bundles, leads to improved long-termcontinence rates after radical prostatectomy. Eur Urol. 2016;69:584–9. https://doi.org/10.1016/j.eururo.2015.07.037

48. Avulova S, Zhao Z, Lee D, Huang LC, Koyama T, Hoffman KE, et al. The effect of nerve sparing status on sexual and urinary function: 3-year results from the CEASAR study. J Urol. 2018;199:1202–9. https://doi.org/10.1016/j.juro.2017.12.037

49. Pavlovich CP, Rocco B, Druskin SC, Davis JW. Urinary continence recovery after radical prostatectomy—Anatomical/reconstructive and nerve-sparing techniques to improve outcomes. BJU Int. 2017;120:185–96. https://doi.org/10.1111/bju.13852

50. Abdollah F, Sun M, Suardi N, Gallina A, Capitanio U, Bianchi M, et al. Presence of positive surgical margin in patients with organ-confined prostate cancer equals to extracapsular extension negative surgical margin. A plea for TNM staging system reclassification. Urol Oncol. 2013;31:1497–503. https://doi.org/10.1016/j.juroncol.2012.04.013

51. Obek C, Louis P, Civantos F, Soloway MS. Comparison of digital rectal examination and biopsy results with the radical prostatectomy specimen. J Urol. 1999;161:494–8.

52. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. Eur Urol. 2017;71:618–29. https://doi.org/10.1016/j.eururo.2016.08.003

53. Partin AW, Kattan MW, Subong EN, Walsh PC, Wojno KJ, Oesterling JE, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. JAMA. 1997 May 14; 277(18):1445–51.

54. Tosoin JJ, Chappidi M, Feng Z, Humphreys EB, Han M, Pavlovich CP, et al. Prediction of pathological stage based on clinical stage, prostate-specific antigen, and biopsy Gleason score: Partin tables in the contemporary era. BJU Int. 2017;119:676–83. https://doi.org/10.1111/bju.13573

55. Ohori M, Kattan MW, Koh H, Maru N, Slawin KM, Shariat S, et al. Predicting the presence and side of extracapsular extension: A nomogram for staging prostate cancer. J Urol. 2004;171:1844–9. https://doi.org/10.1016/j.juro.2003.01.085

56. Steuber T, Graefen M, Haese A, Erbersdobler A, Chun FK, Schlot T, et al. Validation of a nomogram for prediction of side specific extracapsular extension at radical prostatectomy. J Urol. 2006;175:939–44. https://doi.org/10.1016/s0022-5347(05)00342-3

57. Cagliannos I, Karakiewicz P, Eastham JA, Ohori M, Rabbani F, Gerick C, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. J Urol. 2003;170:1798–803. https://doi.org/10.1097/01.ju.0000019805.98960.13

58. Prostate Cancer Nomograms: Pre-Radical Prostatectomy Preparation and needle biopsy tool to predict probability of extraprostatic extension in prostate cancer patients. Memorial Sloan Kettering Cancer Center. https://www.mskcc.org/nomograms/prostate/pre_op
59. Tanaka K, Shigemura K, Muramaki M, Takahashi S, Miyake H, Fujisawa M. Efficacy of using three-tesla magnetic resonance imaging diagnosis of capsule invasion for decision-making about neurovascular bundle preservation in robotic-assisted radical prostatectomy. Korean J Urol. 2013;54:437–41. https://doi.org/10.4111/kju.2013.54.7.437

60. Radtke JP, Hadaschik BA, Wolf MB, Freitag MT, Schwab C, Alt C, et al. The impact of magnetic resonance imaging on prediction of extraprostatic extension and prostatectomy outcome in patients with low-, intermediate- and high-risk prostate cancer: Try to find a standard. J Endourol. 2015;29:1396–405. https://doi.org/10.1089/end.2015.0358

61. de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM. Accuracy of magnetic resonance imaging for local staging of prostate cancer: A diagnostic meta-analysis. Eur Urol. 2016;70:233–45. https://doi.org/10.1016/j.eururo.2015.07.029

62. Jansen BHE, Nieuwenhuizen JA, Oprea-Lager DE, et al. Adding multiparametric MRI to the MSKCC and Partin nomograms for primary prostate cancer: Improving local tumor staging? Urol Oncol. 2019;37:181.e1–6. https://doi.org/10.1016/j.juro Onc.2018.10.026

63. Weaver JK, Kim EH, Vetter JM, Fowler KJ, Siegel CL, Andriole GL. Presence of magnetic resonance imaging suspicious lesion predicts Gleason 7 or greater prostate cancer in biopsy-naive patients. Urol. 2016;88:119–24. https://doi.org/10.1016/j.jurology.2015.10.023

64. Lepor H, Tareen B. Neurovascular bundle resection: Does it improve the margins? Urol Oncol. 2010;28:215–8. https://doi.org/10.1016/j.juro Onc.2009.08.014

65. Stolzenburg JU, Kalidonis P, Do M, Dietel A, Häfner T, Rabenalt R, et al. A comparison of interfaces for interfascial and intrafascial nerve-sparing radical prostatectomy. Urology. 2010;76:743–8. https://doi.org/10.1016/j.jurology.2010.03.089

66. Steineck G, Bjartell A, Hugosson J, Axén E, Carlsson S, Strange J, et al. LAPPRO steering committee. Degree of preservation of the neurovascular bundles during radical prostatectomy and urinary continence 1 year after surgery. Eur Urol. 2015;67:559–68. https://doi.org/10.1016/j.eururo.2014.10.011

67. Shikanov SA, Zorn KC, Zagaja GP, Shalhav AL. Trifecta outcomes after robotic-assisted laparoscopic prostatectomy. Urology. 2009;74:619–23. https://doi.org/10.1016/j.jurology.2009.02.082

68. Moris L et al. Oncological outcome after nerve-sparing versus non-nerve sparing radical prostatectomy in non-metastatic prostate cancer: a systematic review. (submitted)

69. Couture F, Polesello S, Thomlomier C, Bondarenko HD, Karakiewicz PI, Nazzani S, et al. Predictors of deviation in neurovascular bundle preservation during robotic prostatectomy. Can J Urol. 2019;26:9644–53.

70. Diamand R, Ploussard G, Roumiguié M, Odera M, Benamran D, Fiard G, et al. External validation of a multiparametric magnetic resonance imaging-based nomogram for the prediction of extracapsular extension and seminal vesicle invasion in prostate cancer patients undergoing radical prostatectomy. Eur Urol. 2021;79:180–5. https://doi.org/10.1016/j.eururo.2020.09.037

71. Fossá SD, Beyer B, Dahl AA, Aas K, Eri LM, Kvan E, et al. Improved patient-reported functional outcomes after nerve-sparing radical prostatectomy by using NeuroSAFE technique. Scand J Urol. 2019;53:385–91. https://doi.org/10.1080/21681805.2019.1693625

72. Beyer B, Schlomm T, Tennstedt P, Boehm K, Adam M, Schiffermann J, et al. A feasible and time-efficient adaptation of NeuroSAFE for da Vinci robot-assisted radical prostatectomy. Eur Urol. 2014;66:138–44. https://doi.org/10.1016/j.eururo.2013.12.014

73. https://clinicaltrials.gov/ct2/show/NCT03317990?term=Neurosafe&cond=prostate+cancer&draw=2&rank=1

74. Boustani AM, Pucar D, Saperstein L. Molecular imaging of prostate cancer. Br J Radiol. 2018;91:20170736. https://doi.org/10.1259/bjr.20170736

75. Porpiglia F, Checcucci E, Amparore D, Manfredi M, Massa F, Pizzolla P, et al. Three-dimensional elastic augmented-reality robot-assisted radical prostatectomy using hyperaccuracy three-dimensional reconstruction technology: A step further in the identification of capsular involvement. Eur Urol. 2019;76:505–14. https://doi.org/10.1016/j.eururo.2019.03.037

76. Ceci F, Oprea-Lager DE, Emmett L, Adam JA, Bomanji J, Czernin J, et al. E-PSMA: The EANM standardized reporting guidelines v1.0 for PSMA-PET. Eur J Nucl Med Mol Imaging. 2021;48:1626–38. https://doi.org/10.1007/s00259-021-05245-y

How to cite this article: Vis AN, van den Bergh RCN, van der Poel HG, Mottrie A, Stricker PD, Graefen M, et al. Selection of patients for nerve sparing surgery in robot-assisted radical prostatectomy. BJUI Compass. 2022;3(1):6–18. https://doi.org/10.1002/bco2.1115