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Abstract

Context: Surgical techniques aimed at preserving the neurovascular bundles during radical prostatectomy (RP) have been proposed to improve functional outcomes. However, it remains unclear if nerve-sparing (NS) surgery adversely affects oncological metrics.

Objective: To explore the oncological safety of NS versus non-NS (NNS) surgery and to identify factors affecting the oncological outcomes of NS surgery.

Evidence acquisition: Relevant databases were searched for English language articles published between January 1, 1990 and May 8, 2020. Comparative studies for patients with nonmetastatic prostate cancer (PCa) treated with primary RP were included. NS and NNS techniques were compared. The main outcomes were side-specific positive

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1. Introduction

Erectile dysfunction and urinary incontinence are the two most frequent long-term side effects of radical prostatectomy (RP) in patients with prostate cancer (PCa). The detrimental impact of surgery on health-related quality of life (QoL) can be mitigated by using techniques aimed at sparing the neurovascular bundles (NVBs), which are responsible for functional outcomes [1,2]. Nonetheless, NVB sparing might increase the risk of positive surgical margins (PSM). Since oncological safety remains a major principle in surgery, nerve-sparing (NS) surgery should only be performed when it does not lead to a worse oncological outcome. The reported prevalence of PSM after robot-assisted RP is approximately 9% (range 4–23%) for organ-confined disease (pT2) but up to 37% (range 29–50%) for pT3 cancers, and this is associated with a higher risk of biochemical recurrence (BCR) [3–5]. Maintaining the right balance between an oncologically safe resection and optimal preservation of patient QoL is challenging and the impact of NS surgery on oncological control is still debated. In the face of such a paucity of data, we aimed to perform a systematic review of the literature to evaluate the oncological safety of NS surgery compared with non-NS (NNS) surgery and identify subgroups in which NS techniques are associated with worse oncological outcomes to allow better counseling of patients and the potential for better risk-adapted surgical strategies.

2. Evidence acquisition

The review was undertaken by the European Association of Urology (EAU) Prostate Cancer Guideline Panel as part of its guideline update for 2021. The protocol for this review was registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO; registration number CRD42020186493). The review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [6] and Cochrane review principles [7]. PICO development was performed by the EAU Prostate Cancer Guideline Panel based on the expertise of urologists, oncologists, radiotherapists, radiologists, pathologists, and a patient representative. The Medline, Embase, and Cochrane controlled trials databases and ClinicalTrials.gov were searched for all relevant English language articles published from January 1990 until May 2020 (Supplementary material). All abstracts and full-text articles were independently screened in duplicate (L.M., G.G., A.V.) and disagreement was resolved via discussion or reference to an independent third party (T.V.D.B.).

The study population was limited to men with histologically proven nonmetastatic PCa (cT1N0M0) who underwent a RP with or without pelvic lymph node dissection as primary treatment. The use of any specific NS technique was compared to any NNS procedure. It is notable that NS was defined per study, with clear variation between studies. The primary outcome was postoperative side-specific positive surgical margins (ssPSM), defined by anatomical side and related to the NS side to provide assurance that margin positivity was indeed related to the surgical technique. Secondary outcomes were persistent prostate-specific antigen (PSA) at 3 mo after RP, BCR (all definitions), the need for any salvage treatment, distant metastasis-free survival, PCa-specific survival, and overall survival. Data extraction and risk of bias (RoB) assessment were performed independently in duplicate. The RoB assessment was based on the Cochrane recommendations for RoB assessment of...
nonrandomized studies (NRSs) [8], comprising the standard Cochrane domains and additional assessment of five key prespecified confounding factors for NRSs [9,10]. Potential subgroup analyses were preplanned for the following variables: EAU risk groups, clinically localized versus locally advanced PCa, biopsy Gleason score (bGS), surgical approach, and NS extent for the NS techniques. Owing to the retrospective nature of the studies included, no formal meta-analysis was planned.

3. Evidence synthesis

3.1. Quantity of evidence identified

The selection process is outlined in the PRISMA flow diagram in Figure 1. In total, 2936 records were identified via database searching, of which 1573 were screened after removal of duplicates. Of these, 75 articles were eligible for full-text screening. Finally, 18 studies met the inclusion criteria [11–27]. Sixteen studies were excluded because side specificity for PSM was lacking [28–43].

3.2. Characteristics of the studies included

A total of 21,654 patients in 18 NRSs were included in this review. The primary outcome of ssPSM was reported in seven studies. BCR as the only secondary outcome identified was reported in 13 studies. Supplementary Tables 1 and 2 present the patient characteristics for studies reporting on PSM and BCR, respectively. In general, the decision to perform NS surgery was based on clinical (digital rectal examination [DRE]), biochemical (PSA), and histopathological (GS/International Society of Urological Pathology [ISUP]) criteria. Clinical T stage was reported according to the TNM classification [44] and therefore based on DRE only. Biopsy strategy was often not described and no study mentioned the use of targeted biopsies. In addition, information on the surgical approach was often missing. Only a few studies included evaluation with multiparametric magnetic resonance imaging (mpMRI) for local staging [13,15,21,23]. Supplementary Tables 3 and 4 report the corresponding outcomes and statistical analyses performed in these studies. No randomized controlled trials (RCTs) were identified in our search process and only one prospective observational study was included [13].

3.3. RoB and confounding assessment for the studies included

Figure 2 summarizes the RoB and confounding assessment for all the studies included. The overall RoB and confounding were high across most domains, with high RoB for selection, performance, detection, attrition, and reporting bias owing to the lack of RCTs. Only a few studies had low to moderate confounding bias for cT stage, bGS, and initial PSA [11,14–17,20,22,27], whereas others did not report or corrected for these variables [12,13,18,19,21,24–26,45,46] (Fig. 3).

![Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart.](https://doi.org/10.1016/j.euf.2021.05.009)
3.4. Results of the evidence synthesis

3.4.1. Selection criteria for NS RP
Since all studies were NRSS, treatment allocation was biased, which had an important impact on the final study results. The overall population receiving any type of NS RP had more favorable tumor characteristics (lower bGS, T stage, and age) compared to the overall NNS group. The criteria for NS RP for nonmetastatic PCa remain unclear and highly diverse (Supplementary Table 5). Twelve of the 18 papers chose specific criteria, but no study used the same criteria or was able to recommend a specific set of characteristics [12–14,16–19,21,23–25,45]. The most frequent criterion for bilateral NS RP was the presence of low-risk disease [13,16,17,24]. Selection for unilateral NS was based on the same but less restrictive characteristics: PSA <10 ng/ml or GS ≤6 or normal DRE at the NS side, with or without information on biopsy core positivity. However, some groups focused solely on the results of prostate biopsies [23,25]. Kumar et al [23] used a threshold of four or more positive cores and DRE results to make their decision, whereas Graefen et al [25] only performed NS RP if all cores from systematic sextant biopsies on the specific side were negative. Preoperative imaging criteria from mpMRI examinations were limited, probably owing to the restricted MRI availability at the time of preoperative assessment. Soeterik et al [15] reported the presence of extraprostatic extension (EPE) on MRI and used this information in their adjusted model to evaluate the impact of NS RP on PSM. However, they failed to provide specific selection criteria for NS RP. Only two studies included MRI results in the decision to perform NS surgery, omitting NS surgery on the side with MRI-defined EPE [15,21]. The other studies did not specify any criteria and left the decision at the discretion of the operating surgeon during the procedure [11,15,20,22,26,27].

3.4.2. Side-specific PSM
Seven studies evaluated the correlation between NS RP and PSM [15,16,20,22,24,25,45]. Four of the seven studies concluded that NS surgery in well-selected patients (Supplementary Table 5) did not increase margin positivity [20,24,25,45] and that NS procedures could be safely performed in these patients. In three of these studies, conclusions were based on results from unadjusted analyses and are therefore prone to biases [24,25,45]. More recently published studies that used adjusted analyses highlighted that NVB preservation might be associated with a higher risk of ssPSM [15,16,22]. Soeterik et al [15] adjusted for side-specific covariates (including NS, DRE, MRI local stage [organ-confined vs EPE], highest biopsy ISUP grade, and percentage core positivity). In their models, NS robot-assisted RP was clearly associated with a higher risk of ssPSM (model 1: odds ratio [OR] 1.53; \( p < 0.001 \); model 2 [accounting for missing data]: OR 1.42; \( p = 0.005 \)). Rader et al [16] included type of surgery to adjust for the effect of surgical approach (open vs robotic) and reported that NS surgery was associated with a higher risk of PSM (OR 1.5, 95% confidence interval [CI] 1.0–2.1; \( p = 0.03 \)). Only one (retrospective) study specifically compared patients with EPE to patients with organ-confined disease [22]. Of the 273 lobes without EPE, none had PSM (0%) when NNS resection was performed, while 9% positivity was observed when NS RP was performed (\( p = 0.02 \)). Patients with EPE had a higher risk of ssPSM (relative risk [RR] 6.31, 95% CI 3.78–10.52) suggesting that a wide resection should be performed in these patients to optimize oncological control. When correcting for preoperative PSA, bGS, prostate volume, tumor volume, and year of surgery, NNS resections remained associated with a lower risk of ssPSM (RR 0.43, 95% CI 0.26–0.71; \( p = 0.001 \)).
In conclusion, on the basis of the more recently published studies with adjustment for important covariates, it appears that NS RP is associated with a higher risk of sPSM. When characteristics for non–organ-confined disease, such as EPE at pathology and MRI findings, are present, the risk of PSM increases. However, even in studies using low-risk PCA features for selection of candidates for NS surgery, a higher risk of PSM after bilateral NS RP was observed. None of the studies included in the review evaluated the risk of PSM in patients with high-risk PCa.
3.4.3. Biochemical recurrence

Thirteen studies reported on the correlation of NS surgery with BCR [11,12,25–27,13,14,17–21,23]. Definitions used for BCR were: prostatectomy (PSA recurrence > 0.2 ng/ml [12–14,17,18,20,21,23,26], > 0.4 ng/ml [11,23,27], or > 0.1 ng/ml for more than two measurements [19]. Data on PSA persistence were not available. No negative impact of NS RP on BCR was observed, with some studies showing lower BCR rates after NS surgery [13,19,20,23]. Patients receiving NS surgery often had more favorable tumor characteristics, with lower cT stage, GS, and tumor load at biopsy (Supplementary Table 5). In general, if any high-risk feature (palpable disease, EPE, or high tumor load at biopsy) was present, NS surgery was not carried out on that side. In the only prospective observational study, in which only patients with low-risk PCa underwent NS RP, NS RP was associated with a lower BCR rate (n = 2; 2%) when compared to NNS RP (n = 16; 12.7%) [13]. The subanalysis by Røder et al. [17] with stratification according to surgical margins showed that NS RP was not associated with an increase in BCR compared to NNS RP in either subgroup (positive or negative surgical margins) at short median follow-up of 3.6 yr (range 0.5–15.5). It is unclear how many patients had intermediate- or even high-risk PCa in both subgroups. Although this could reflect the uneven distribution of patients with low-risk PCa in the NS RP group, it might suggest that PSM per se does not carry the same risk of recurrence [47]. As studies reported to date largely involved men with low-risk disease, care should be taken when applying these findings to current surgical cohorts with an increasing percentage of patients with high-risk PCa.

3.4.4. BCR in high-risk PCa

Three papers specifically focused on high-risk PCa [12,21,23], a subgroup for which NS surgery is more controversial and oncological control of utmost importance. None of these studies showed an increase in the risk in BCR after NS RP over median follow-up of 12.5 mo [21] and 25 mo [12,23]. Kumar et al. [23] reported the lowest rate of BCR for patients treated with bilateral NS surgery (9.3% vs 10.3% unilateral NS vs 18.6% NNS; p = 0.01). However, since each study on high-risk PCa used different selection criteria and no study performed adjusted multivariate analyses, it remains difficult to assess the factors that increase the risk of BCR with NS RP. In every study, each prostate lobe was evaluated separately so that the degree of NS could be adapted according to the extent of the disease on each side. In general, if any high-risk feature (palpable disease, number of biopsy cores involved, or clear EPE on MRI) was present, NS RP was omitted on that specific side.

3.5. Discussion

3.5.1. Principal findings

Surgery is an effective treatment option for patients with localized PCa [48,49] and represents a recommended therapeutic option for patients with intermediate- or high-risk PCa with life expectancy of > 10 yr [47]. The description of the peri-prostatic NVBs and their preservation revolutionized the surgical management of localized PCa [50], even in the absence of level 1 evidence. However, the decision for NVB preservation is a balance between oncological control and functional outcomes [2]. In particular, NS surgery might transect the prostate or cause PSM in a region of EPE because of dissection planes close to the prostatic capsule. Achieving negative surgical margins is deemed important [3,4] because PSM at final pathology might result in an increase of the risk of recurrence and a need for adjuvant/salvage therapies, with the additional risk of cumulative side effects [3,4,51]. This might eventually compromise the benefits of NS RP [52,53]. Since the impact of NS surgery on oncological control in patients with PCa is still debated, we aimed to systematically evaluate the effects of NVB preservation on the risk of PSM and oncological outcomes.

3.5.2. Effect on PSM

Our systematic review revealed an association between NS surgery and higher risk of ssPSM on the basis of studies that used analyses adjusted for side-specific confounders. Three papers did report a lower risk of ssPSM after NS RP but did not allow for a comprehensive evaluation of the impact of NS surgery owing to a lack of adjusted analyses [24,45,54]. Causality between NS side and PSM should be determined with each prostate lobe evaluated separately and adjustment for side-specific local tumor characteristics [15,20,22]. On the basis of the criteria used to perform NS surgery, the majority of the patients undergoing NS surgery (especially bilateral NS) probably had indolent, insignificant tumors, which should be managed with active surveillance rather than radical treatment. It should be noted that not every PSM is the same and the current evidence did not specify the PSM extent or the tumor characteristics at the side of the PSM, which could have an impact on further patient management. However, our observations of a higher rate of ssPSM in a mainly low-risk patient population raises a major question concerning NS RP safety in patients with higher risk.

3.5.3. Effect on BCR

We also assessed the impact of NS RP on BCR as the sole secondary outcome of interest identified. BCR might be considered a surrogate endpoint for stronger oncological outcomes and might be related to the presence of PSM [3,4], although BCR may be slower to appear in men with low-risk PCa. Interestingly, none of the studies included reported a negative impact of NS RP on BCR. Some studies even reported a lower rate of BCR after a complete NS RP [13,20,23]. This observation can be explained by the very short follow-up and selection bias, with more low-risk patients undergoing NS surgery. The studies on high-risk PCa that were included suggest that NS RP can be performed without increasing the risk of BCR when adapting the extent of NS surgery according to predefined features such as cT stage, EPE, and histopathological criteria [12,21,23]. Both Takahara et al. [12] and Kumar et al. [23] used a combination of clinical and pathological characteristics in selecting candidates for NS surgery. Both studies concluded that an NS technique might result in equivalent oncological control
compared to NNS, although follow-up was very short (median 12.5–25 mo). A recently published study confirmed the feasibility and oncological safety of NS RP compared to NNS RP for patients with high-risk PCs [55]. Besides favorable BCR, they reported better overall and PCA-specific survival with NS surgery. However, the study had a retrospective design with the intrinsic risk of residual selection bias whereby surgeons select cases with unfavorable tumor characteristics for NNS surgery. Moreover, these results are based on patients treated in two very high-volume centers with excellent expertise and systematic use of the NeuroSafe technique. Therefore, the results might not be applicable to other centers or other techniques.

3.5.4. Principles of NS surgery

Our data show that NS procedures are not an “all or none” phenomenon. Several different NS techniques can be offered, all of which are technically complex with challenging reproducibility, and expertise is mandatory. Only five of the studies we included specified the NS approach used, all of which were interfascial NS surgery [13,15,18,21,45]. A systematic review comparing intrafascial versus interfascial NS RP concluded that an intrafascial NS technique yielded better functional and oncological control [56]. However, selection bias was present, with patients having high-risk features undergoing wider resections. Owing to the close proximity of the anatomical structures of the NVB, identifying the correct plane is difficult. Heterogeneous anatomical nomenclature for these structures complicates the execution of the desired approach even further [57], which limits the reproducibility [57,58]. As most RP procedures are currently performed robotically, it is likely that those designated as NNS still preserve more of the NVB than before the era of Walsh’s NS surgery. This will impact future research, as a standard definition of NS surgery is lacking. The reality is that the majority of surgeons already practice judicious patient selection for NS surgery and the role of surgical volume and expertise in this selection is of utmost importance. Moreover, it is not uncommon for surgeons to adjust their initial strategy according to perioperative findings, which should only be done by experienced surgeons. An unfavorable impact of NS on BCR is more likely to be found for cases with high-risk disease and/or EPE at the specific side. However, this can be influenced by the preoperative technique used for staging, whether conventional imaging or MRI and its interobserver variability [59]. Besides EPE, other clinical features (cT stage) and pathological criteria (ISUP, number and volume of positive cores) can guide surgeons in their decision-making [60]. Critical clinical judgment is required for individual patients by an experienced urologist balancing the risks and benefits of NS surgery. Criteria suggested by the studies included in the review appear to focus on identifying low-risk disease, and may be supplemented in the future with the widespread introduction of mpMRI.

3.6. Implications for clinical practice and further research

One of the main observations of our systematic review is that NS RP is an underevaluated procedure in patients with intermediate- and high-risk PCa who benefit most from radical treatment. Better defined and objective criteria or nomograms are needed to select these patients for unilateral or bilateral NS RP, which should be revised in the light of current recommendations for local treatment and technical advances. Research should focus on acquiring level 1 data on the functional benefit of NS, optimizing NS techniques, and improving identification of selection criteria. For ethical reasons, it is not likely that RCTs comparing NS versus NNS RP will be designed. However, prospective multicenter studies of good methodological quality and with long-term follow-up for patients with intermediate- and high-risk PCa are needed to identify the ideal patients for NS RP. Large enough sample sizes with multivariate analyses adjusted for side-specific confounders might provide us with a better insight into the risk factors for PSM, BCR, and hard endpoints such as overall and PCA-specific survival. Evaluation of the specific locations of PSM should be the subject of future research, as this is under-reported in the current literature. Not every PSM is meaningful and recurrence-free survival after PSM is frequently observed. A deeper understanding of the location of PSM and linked to the side of NS could provide us with essential information to optimize our NS techniques.

3.6.1. Role of imaging

Recent studies assessing the role of modern imaging techniques are ongoing and may change clinical decision-making. These were clearly lacking in the papers we identified. First, preoperative mpMRI can improve patient selection by better assessing EPE. Studies report a change in surgical plan (more or less radical) in 30–50% of cases [61,62]. A recent systematic review showed that mpMRI was able to modify the extent of NS surgery in 35% of patients, with a more aggressive resection in 63% and a more preservative resection of the bundle in 37% of these cases [63]. Moreover, decisions on whether to perform bilateral or unilateral NS surgery on the basis of mpMRI appear to be correct in 95.9% and 87.5% of cases, respectively [64]. However, this means that the inter-reader variability of mpMRI needs to be acceptable. With the recently published update of Prostate Imaging-Reporting and Data System v2, an improvement in the reproducibility of mpMRI between radiologists is anticipated [65].

3.6.2. Role of perioperative NVB assessment

Apart from imaging, perioperative tools include, among others, augmented-reality three-dimensional models and real-time in vivo techniques for perioperative imaging and guidance, indocyanine green (ICG) staining for NVB visualization, and the neurovascular structure-adjacent frozen section examination (NeuroSAFE) technique to assess PSM during NS procedures [46,62,66]. Results for some of these techniques are still premature, and no functional outcomes or long-term oncological outcomes are available. In the NeuroSAFE technique, the entire NVB-adjacent prostatic tissue is dissected and assessed for PSM perioperatively, with adjustment of the NS technique on the basis of these results [67,68]. The technique has high sensitivity of 93.5% and specificity of 98.8%. Data from the Martini Clinic
highlighted that NeuroSAFE use increased the frequency of NS surgery, lowered PSM rates, and improved functional outcomes, even for non–organ-confined tumors [69,70]. However, besides being a time- and resource-consuming technique, only PSMs beside the NVB are evaluated, with the risk of missing PSMs in other locations. For the use of ICG perioperatively, data remain scarce. ICG use has the potential to visualize the prostatic artery, which runs medi ally to the NVB in up to 100% of cases and can be used to improve localization and safe dissection of the NVB [46,71]. The final effect on surgical margins remains to be evaluated.

As our techniques evolve, the impact on both oncological and functional outcomes will shift, and constant critical reevaluation will be needed. Meanwhile, up-to-date clinical knowledge and surgical experience remain paramount in decisions on the correct approach.

3.7. Limitations and strengths

The review elements were developed in conjunction with the EAU methods committee and a multidisciplinary panel of experts (EAU Prostate Cancer Guideline Panel) including a patient representative. This review was performed in a robust manner in accordance with recognized standards, with a broad search strategy designed by a statistician (C.Y.). Limitations include the retrospective nature of all the studies and the overall significant clinical and methodological heterogeneity across studies, which limited the quality of the data. This introduces a considerable bias, whereby a population of patients with less aggressive disease characteristics is typically considered for NS surgery. Moreover, every study used specific criteria to select patients for NS procedures or failed to specify them, leaving it at the discretion of the surgeon at the time of surgery. Our observations and conclusions are based on studies with short follow-up and mainly patients with low-risk disease, who should generally be managed with active surveillance. Patients with intermediate- and high-risk PCA, who are the target population for NS RP, are underrepresented in this review. Finally, most of these data are based on systematic biopsies without preoperative mpMRI.

4. Conclusions

Current data show an association between NS surgery and higher risk of sPSM. Although this did not increase the risk of BCR in the studies included, it raises the possibility that this technique may increase oncological risk, especially in higher-risk groups over longer follow-up. Caution is required when discussing NS surgery with patients, as it remains a challenging surgical technique. We recommend focusing on generating higher-quality data from multicenter, prospective trials and long-term follow-up in intermediate- and high-risk PCa. In particular, standardized definitions and descriptions of NS surgery must be agreed on and utilized. Until then, the true value of NS surgery in balancing functional benefits against oncological risks will remain uncertain.

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Appendix A. Supplementary data

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