

A Systematic Review of the Effects of Nerve Sparing during Radical Prostatectomy

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This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (2009). MEDLINE, EMBASE, The Cochrane Library, Health Technology Assessment Database, and Web of Science were searched from 1966 to December 2015, yielding 60 records.

RCTs and other controlled or comparative studies were eligible for inclusion. Studies reporting on at least one of the following outcomes, positive surgical margins, continence and potency with data available for nerve sparing and non-nerve sparing groups were included. 16 studies were available for final analysis and included 16269 participants.

Primary outcomes analysed where positive surgical margins and functional outcomes (continence and potency).

Comparing nerve sparing with non-nerve sparing prostatectomy, the proportion of cases resulting in incontinence is lower for nerve sparing prostatectomy.

The proportions of cases resulting in impotence were 0.92 (CI: 0.88 – 0.96) for non-nerve sparing operations, 0.43 (CI: 0.40 – 0.46) for all nerve sparing operations, 0.59 (CI: 0.51 – 0.67) for unilateral and 0.39 (CI: 0.35 – 0.42) for bilateral nerve sparing.

With regards to positive margin rates, these are higher for T3 cancers than for T2 cancers, both for operations that used nerve sparing and for those that did not. For T2 cancers there is little or no difference in the proportion of cases resulting in positive margins for operations with and without nerve sparing. For T3 cancers the proportions of cases with positive margins were practically the same for operations with and without nerve sparing.

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Excluding non-melanoma skin cancer, prostate cancer is the leading cancer diagnosis in men worldwide and the most common cause of cancer related death. The U.S. Cancer Statistics Working Group published prostate cancer incidence and mortality statistics for 2013, 176,450 men were diagnosed with prostate cancer in the United States, with 27,681 patients dying from prostate cancer.¹

For newly diagnosed men, radical prostatectomy offers an excellent prospect of cancer cure.² To standardise the assessment of oncological and functional outcomes after radical prostatectomy the trifecta system was proposed with optimal outcomes being defined as a PSA level of less than 0.2ng/ml, potency sufficient for intercourse with or without pharmacological agent and zero pad use.³ The trifecta outcome can be achieved in 62-70% of patients in centres of excellence.⁴

The description of the course of the cavernous nerve by Walsh and Donker in 1982⁵ proved to be the basis for the development of nerve sparing technique which has resulted in improved post operative potency rates. The association between nerve sparing and continence outcomes is not so clear and is still a matter of debate. Traditional teaching does not support an anatomical relation between nerve sparing and preservation of urinary continence, as the urinary rhabdosphincter is innervated somatically by the extra-pelvic pudendal nerve, and this should not be influenced by nerve sparing. Some authors have attributed an enhanced post-prostatectomy continence rate to a possible intra-pelvic innervation to the rhabdosphincter⁶ and meticulous apical dissection in nerve sparing technique, rather than the preservation of the neurovascular bundles themselves.⁷

The proximity of the posterolateral prostate to the neurovascular bundles inevitably results in a conflict between the desire to preserve functional outcomes and the risk of positive surgical margins (PSM) and biochemical recurrence. The association between nerve sparing and PSM is difficult to ascertain, with patient selection based on biopsy and imaging characteristics confounding a true association between the two. Because pre-operative assessment suffers from limitations in predicting early extra-capsular extension, some authors recommended intra-operative frozen section with excision of the bundle in the event of a positive froze section analysis, and have shown a reduction of PSM with this approach.⁸

The primary aim of this study was to conduct a review of the association between nerve sparing in radical prostatectomy and its association with outcomes of continence, potency and PSM.

METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.(2009) MEDLINE, EMBASE, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register), Health Technology Assessment Database, and Web of Science (science and social science citation index) were searched up to December 2015.

The following terms were searched: ["prostate cancer AND prostatic neoplasms"] AND ["prostatectomy AND radical prostatectomy"] AND ["continence AND urinary incontinence"] AND ["potency AND erectile function AND sexual function"] AND ["margins AND PSM"].

The search strategy did not include or exclude papers based on the surgical approach utilised (open, laparoscopic or robotic) or whether the prostatectomy was combined with a pelvic lymph node dissection or not. No attempt was made to distinguish between different types of nerve sparing, such intra or interfascial dissection. None of the studies included in the analysis made use of sural nerve grating as a method of nerve preservation.

RCTs and other controlled or comparative studies were eligible for inclusion. Studies reporting on at least one of the following outcomes, PSM, continence and potency with data available for nerve sparing and non-nerve sparing groups were included. Only studies where the full original paper was available where included in the final analysis. Studies in languages other than English were excluded. Manual searching of reference lists of relevant publications was performed to identify additional potentially relevant studies. When multiple publications were identified from the same institution and overlapping data sets were used, the publication with the most recent data was included. Any disagreements on study selection or eligibility were resolved with consultation and discussion with a third author.

Two independent authors screened the titles and abstracts obtained. The full text of relevant publications was retrieved for review and included in the analysis if they satisfied the criteria outlined previously. The total number of participants and events were extracted for pooled analysis. Where data was presented as a percentage the raw numbers were calculated. Where more than outcome for continence and

potency was reported at different points of the post-operative follow up, the results at most frequently reported outcome were included, most commonly outcomes at one year after surgery.

All statistical analyses and Forest plots were programmed by RG using R software, version 3.2.5.

RESULTS

Initial search yielded 132 records. After exclusion of duplicates, papers not relevant to this review and papers published in languages other than English, 16 studies were included in the final analysis. A total of 16,023 prostatectomy operations were included in this systematic review. The characteristics of these studies are presented in [Table 1](#).

In all of these studies, nerve sparing treatments were not randomised between patients, but were chosen by specific protocols of the different surgeons. Margin status was assessed after each operation, while continence and potency were assessed in post-operative follow up. No randomised controlled trials were identified which addressed the questions of this review.

Study samples range from 44 (study 9) to 6120 (study 10). The studies were published between 1989 and 2015. In most studies patients underwent open retropubic prostatectomy, although laparoscopic and robot assisted-laparoscopic prostatectomy was also used in some studies. In most the studies the authors present data stratified in non-nerve sparing, unilateral nerve sparing and bilateral nerve sparing groups, in some case this data are presented in two groups, non-nerve sparing and nerve sparing cohorts without distinction being made between unilateral and bilateral nerve sparing cases.

The technique, extent and quality of nerve sparing is not formally accounted for in most of the studies. In one study the definition of nerve sparing was more precisely defined as at least 70% of the neurovascular bundle preserved but this does not take into account damage to microscopic nerves which would not be visible to the surgeon.¹¹

Baseline patient and tumour characteristics were not available in all studies, making assessment of selection bias difficult. In those studies, where such data are available, a selection bias is evident with patients undergoing a nerve sparing procedure having a more favourable clinical stage.

Outcome evaluation was variable in between studies with definitions of potency and continence and

timing of reported outcomes differing significantly. The most common definition of continence was a patient reported no pad use or use of one pad at one year, whilst potency was most commonly defined as the patient reported erections sufficient for vaginal penetration with or without pharmacological aids. The timing of potency recovery differed between studies ranging from 12 to 24 months. In the case of studies reporting on PSM, the definition was uniformly reported as tumour at the inked surface of the prostatectomy specimen.

For each study (subject to the availability of data noted above) we present sample sizes along with the numbers and proportions of cases resulting in each outcome, separately for operations with and without nerve-sparing. For the outcome 'PSM' the numbers and proportions are further classified by cancer type (T2 or T3). Comparisons between the proportions of operations with and without nerve sparing are calculated as risk ratios (RRs) with 95% confidence intervals (CIs). The estimated risk ratios are presented in the form of forest plots on a logarithmic scale, where the size of the symbol (square) is proportional to the precision of the estimate, horizontal lines represent 95% confidence intervals, and a vertical line indicates $RR = 1$ (i.e., no difference in risk between operations with and without nerve sparing).

Some of studies included separate data for unilateral and bilateral nerve sparing operations. These were pooled into one group when comparing outcomes with and without nerve sparing. In addition, for those studies, a secondary analysis comparing outcomes between unilateral and bilateral nerve sparing operations were performed.

The definitions of incontinence and impotence used in outcome evaluation are not standardised across studies. A few studies used validated questionnaires with patient-reported outcomes being the most common method. Also, the baseline pre-operative functional status is not reported in most studies. Formal assessment of quality of life after surgery is not performed in conjunction with continence or potency outcomes in most of the studies included.

Technical factors known to have an impact on continence outcomes, such as bladder neck sparing technique, membranous urethral length and different methods of anastomosing the bladder to the urethra and reconstruction, are not described or reported and therefore not the subject of the study.

Table 1 *Characteristics of included studies*

	Authors	Date of publication	Sample Size	Surgical Approach	Age, years	Comparison Groups
1	Finan et al	1989	68	Retropubic	Mean $\pm$ SD 64.3 $\pm$ 4.9	NNS, BNS
2	Catalona et al	1993	784	Retropubic	Mean $\pm$ SD 64.2 $\pm$ 7.02	UNS, BNS
3	Dalkin et al	2000	170	RRP	NA	NNS, UNS
4	Lu et al	2003	44	RRP	Mean $\pm$ SD 68.7 $\pm$ 4.5	NNS, UNS, BNS
5	Tsujimura et al	2004	135	RRP	Mean $\pm$ SD NNS: 68.1 $\pm$ 0.7 UNS: 67.2 $\pm$ 1.3 NNS: 66.4 $\pm$ 1.5	NNS, UNS, BNS
6	Huland et al	2005	723	RRP	Mean $\pm$ SD NNS: 63.37 $\pm$ 5.93 NS: 61.43 $\pm$ 5.78	NNS, UNS, BNS
7	Studer et al	2006	536	RRP	Mean (IQR) 64 (58 - 68)	NNS, UNS, BNS
8	Zippe et al	2008	156	RRP	Mean $\pm$ SD 64.1 $\pm$ 6.7	NNS, UNS, BNS
9	Lepor et al	2008	1110	RRP	Mean 58.4	NNS, UNS, BNS
10	Hu et al	2010	602	RALP	Mean NNS: 60.5 UNS: 59.0 BNS: 57.8	NNS, UNS, BNS
11	Patel et al	2010	876	RARP	Median (IQR) 61 (56 - 66)	NNS, UNS, BNS
12	Trachtenberg et al	2010	856	RRP, LRP	Mean NNS: 63.4 NS 60.2	NNS, NS
13	Striker et al	2011	945	RRP	Mean NNS: 64.2 UNS 62.3:BNS 59.6	NNS, UNS, BNS
14	Briganti et al	2012	1249	RRP	Mean (Range) 63.8 (39-85)	NNS, UNS, BNS
15	Iversen et al	2014	1649	RRP	Mean (Range) 63 (59 - 66)	NNS, UNS, BNS
16	Cagiannos et al	2014	6120	RRP, LRP, RALP	Mean $\pm$ SD 59.2 $\pm$ 7.1	NNS, UNS, BNS

Urinary continence outcomes

Figure 1 summarises the data for urinary incontinence. Five studies (1, 7, 8, 13 and 14) were included in the comparison between nerve sparing and non-nerve sparing groups. The total number of patients was 2616, with 578 having non-nerve sparing operations and 2038 having nerve sparing operations. One study (study 9) did not report on a non-nerve sparing group but was included in a separate analysis comparing unilateral nerve sparing with bilateral nerve sparing outcomes. In this analysis five studies (7, 8, 9, 13 and 14) were included, with a total of 567 patients having had a unilateral nerve sparing procedure and 2048 patients undergoing a bilateral nerve sparing prostatectomy. Study 1 was excluded from this analysis as it did not report separate outcomes for unilateral and bilateral nerve sparing procedures.

Comparing nerve sparing with non-nerve sparing prostatectomy, for each of the five studies, the proportion of cases resulting in incontinence is lower for nerve sparing prostatectomy. The proportions range from 0.14 and 0.55 for non-nerve sparing operations, and from 0.04 to 0.21 for nerve sparing operations. Except for Study 13, the 95% confidence intervals for the risk ratios do not include $RR = 1$, and the five risk ratios are consistent with a common value. The weighted average RR is 0.40 (CI: 0.35-0.46) with nerve sparing having the lower risk.

Comparing bilateral with unilateral nerve sparing, for the three smallest studies (6, 8 and 9) the proportions of incontinent patients are small and are consistent with $RR = 1$. For the two larger studies (13 and 14) the proportions are clearly lower for bilateral nerve sparing. All five risk ratios are consistent with a common value: the weighted average RR is 0.59 (CI: 0.45 – 0.77) with bilateral nerve sparing having the lower risk.

Potency outcomes

Five studies (2, 3, 4, 5, and 9) were included in the analysis comparing potency outcomes, which is summarised in **Figure 2**. Studies 2 and 9 were excluded in the analysis comparing nerve sparing with non-nerve sparing technique as no non-nerve sparing data were reported. Similarly, study 3 was not included in the comparison between unilateral and bilateral nerve sparing as it did not report outcomes for these separately.

For non-nerve sparing operations, the proportions of cases resulting in impotence are very similar and are consistent with a common proportion for all five studies. Similar consistency is seen for nerve sparing operations, and likewise when considering unilateral and bilateral nerve sparing operations separately. The risks of impotence are therefore well summarised by pooling the counts across all studies

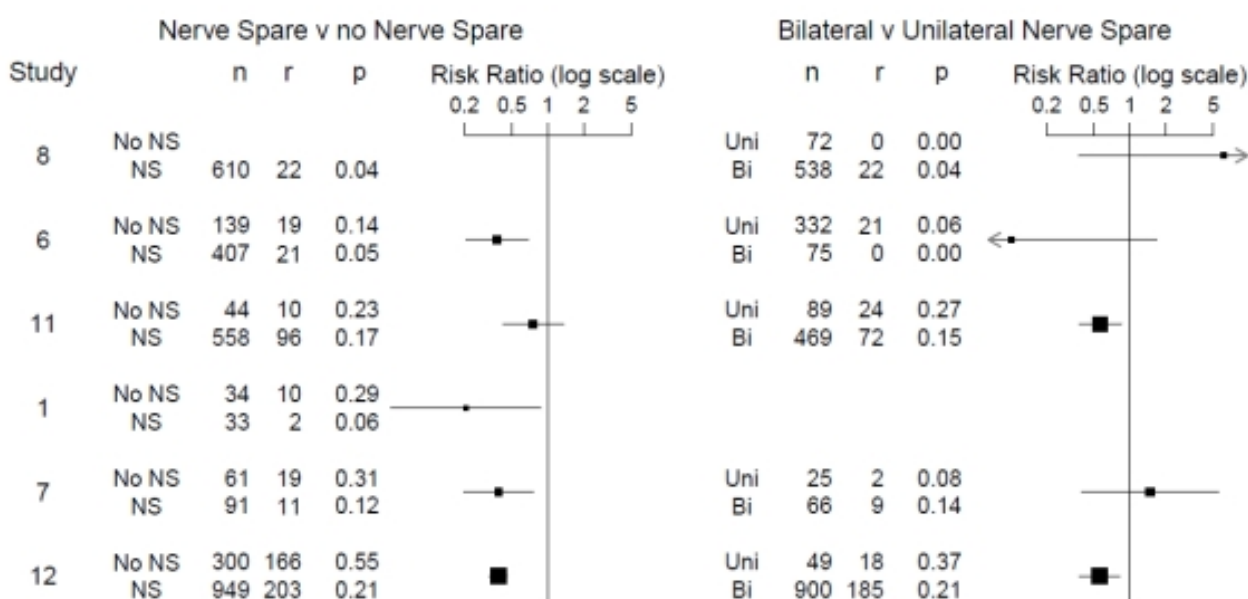


Figure 1 Summary data and forest plots of the relative risk of incontinence (with 95% confidence intervals) for operations with and without nerve sparing, and with bilateral compared with unilateral nerve sparing, for six studies (Table 1): n denotes the number of operations, r is the number with outcome "incontinent" and $p = r/n$ is the proportion incontinent. Studies are listed by increasing order of p for non-nerve sparing operations. Study 9 did not include non-nerve sparing operations and study 1 did not report separate data for unilateral and bilateral nerve sparing.

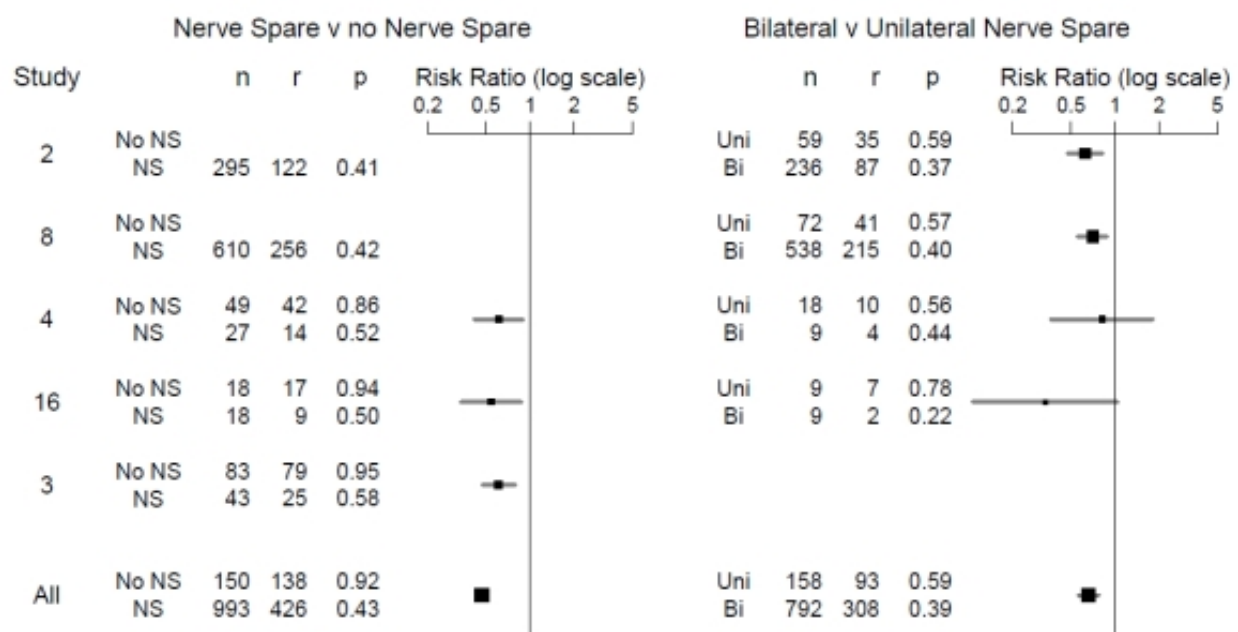


Figure 2 Summary data and forest plots of the relative risk of impotence (with 95% confidence intervals) for operations with and without nerve sparing, and with bilateral compared with unilateral nerve sparing, for five studies (Table 1): *n* denotes the number of operations, *r* is the number with the outcome “impotent” and *p* = *r*/*n* is the proportion of impotent subjects. Studies are listed in increasing order of *p* for non-nerve sparing operations. Studies 2 and 9 did not include non-nerve sparing operations, and study 3 did not report separate data for unilateral and bilateral nerve sparing procedures. For each category of operation, the data are consistent with the same risk of impotence in each study, and the last two rows give pooled data across all five studies.

for each type of operation (see last two rows in Figure 2).

Overall, the proportions of cases resulting in impotence were 0.92 (CI: 0.88 – 0.96) for non-nerve sparing operations, 0.43 (CI: 0.40 – 0.46) for all nerve sparing operations, 0.59 (CI: 0.51 – 0.67) for unilateral and 0.39 (CI: 0.35 – 0.42) for bilateral nerve sparing. These substantial improvements in sexual potency and the direct correlation between post-prostatectomy sexual function and degree of nerve sparing suggests neurovascular preservation as a primary determinant of potency.

PSM outcomes

Seven studies (6, 10, 11, 12, 13, 15, and 16) were included in our analyses comparing positive margin rates after nerve sparing and non-nerve sparing prostatectomy. In these studies, 2593 patients underwent non-nerve sparing resection and 9867 patients underwent a nerve sparing procedure. Because margin outcomes are likely to depend on the type of cancer, we consider these separately for T2 and T3 cancers. The results are presented in Figure 3. The main features are:

- For every study, the proportion of operations resulting in PSM is higher (generally substantially higher) for T3 cancers than for T2 cancers, both for operations that used nerve sparing and for those that did not.
- For T2 cancers there is little or no difference in the proportion of cases resulting in PSM for operations with and without nerve sparing. The risk ratios are plotted as open squares with 95% confidence intervals, which are also given numerically. They are individually consistent with RR = 1, as well as being consistent with a common RR for all studies.
- For T3 cancers: for the bottom five studies (10, 11, 12, 13, and 15) the proportions of cases with PSM were practically the same for operations with and without nerve sparing and consistent with a common risk ratio of 1. But for studies 6 and 16, the proportion with PSM was clearly lower when nerve sparing was used.

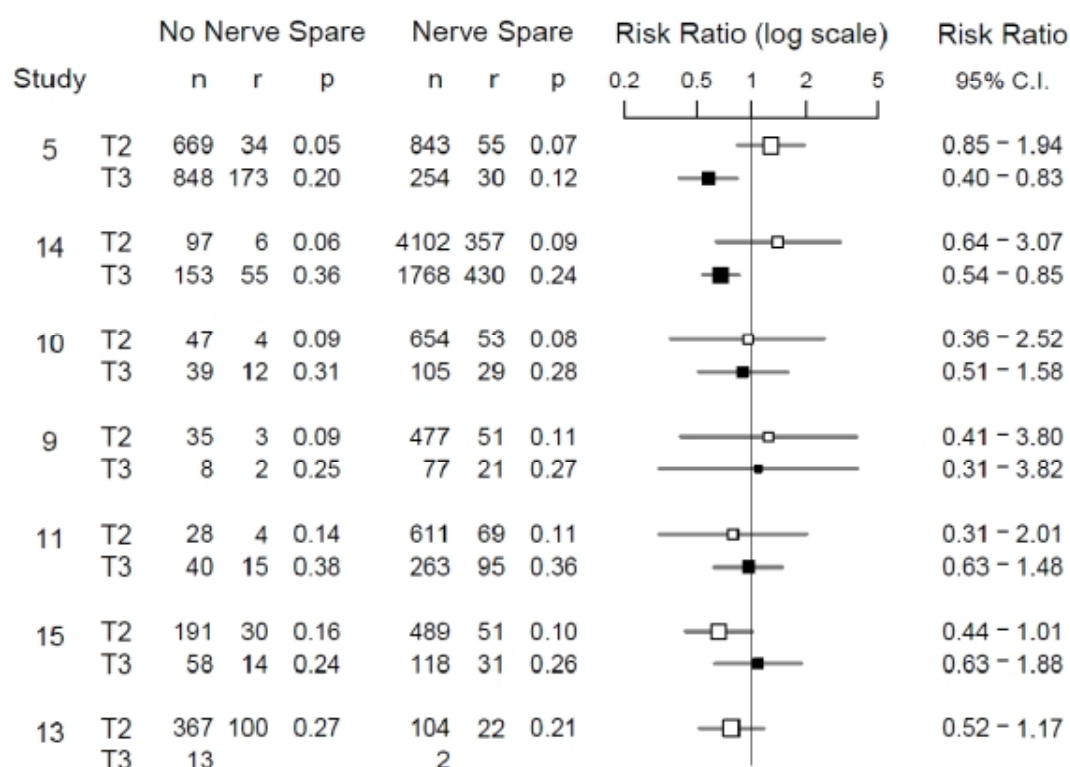


Figure 3 Summary data and forest plots of the relative risk of PSM (with 95% confidence intervals) for operations with and without nerve sparing, for each of the two cancer types (T2 and T3) for seven studies (see table 1): n denotes the number of operations, r is the number with outcome “positive surgical margin” (PSM) and $p = r/n$ is the proportion resulting in PSM. Studies are listed in increasing order of p for non-nerve sparing operations on T2 cancers. Study 15 did not report PSM outcomes for 15 operations on T3 cancers.

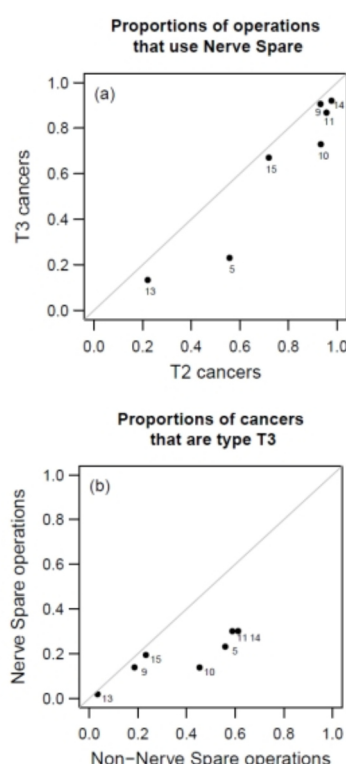


Figure 4 (A) The proportion of nerve sparing operations for T3 cancers plotted against corresponding proportion for T2 cancers, for the seven studies in Figure 1. (B) The proportion of T3 cancers among nerve sparing operations plotted against corresponding proportion among non-nerve sparing operations for the same seven studies.

It is to be expected that the proportion with PSM is higher for T3 than for T2 cancers, and interesting that even for T3 cancers, PSM do not seem to be more frequent following nerve sparing surgery (and indeed are less frequent for studies 6 and 16). For T3 cancers, positive margin risks are not expected to be affected by nerve sparing for anterior and apical tumours, but because the location of the tumour is not reported in any of the studies it is difficult to assess whether tumour location influenced these results.

Figure 4 shows an association between the use of nerve sparing and the type of cancer (T2/T3). In Panel A, the proportion of operations that used nerve sparing ranges from 0.13 to 0.98 for different studies, but nevertheless is always lower for T3 than for T2 cancers. Likewise, in Panel B, the proportion of cancers that are type T3 ranges from 0.02 to 0.61 but is always lower when nerve sparing was used. This possibly reflects good operative selection of patients for nerve sparing, although in studies 10, 12 and 15 the proportions of T3 cancers were similar for operations with and without nerve sparing. In study 10, for example, a high proportion of operations used nerve sparing, but low proportion of cancers were T3 cancers (panel B).

In this systematic analysis, we analysed the effect of sparing the neurovascular bundle on post-operative continence, potency and positive margin rates.

Post prostatectomy continence outcomes are significantly better in patients undergoing nerve sparing procedures. The pathophysiological basis for this remains a matter of debate. In one of the papers, nerve sparing procedures were associated with a longer urodynamic functional urethral length post-prostatectomy, this probably independently contributing to better continence outcomes.¹² In a large German series, where the authors use frozen section neuroSAFE technique, they conclude that it is meticulous apical dissection and preservation of anatomical structures in the vicinity which contribute to continence rather preservation of the NVB that results in better continence outcomes.⁸ This correlates with the results of this review, where a significant difference in continence rates was detected between nerve sparing and non-nerve sparing operations, however there is only very little additional benefit with bilateral nerve sparing compared to unilateral nerve sparing, indicating that this benefit is not directly related to the degree of cavernosal nerve preservation. It may be that limited use of diathermy around the urethra and seminal vesicles as is standard during nerve sparing prevents damage to somatic nerves associated with the maintenance of continence.

The results for potency rates are also in favour of nerve sparing, with similar and consistent patterns across all the studies. There exists a significant benefit in post-operative sexual function comparing non-nerve sparing, unilateral nerve sparing and bilateral nerve sparing procedures, indicating that the degree of preservation of the NVBs is the main determinant of post prostatectomy erectile function. Although it is the preservation of the neural component that is the general thought to be responsible for erectile function, tumescence is also a vascular phenomenon and preservation of the vascular component might also contribute to improved potency rates after surgery for prostate cancer.

The results for positive margin rates are perhaps less subject to potential reporting biases compared to those for the functional outcomes. The definition of positive margin is uniform across studies and more robust being less subjective and not subject to influence by the timing of reporting. However, although margin status does correlate with

oncological results after surgery, standardised reporting using the Trifecta system uses post-operative PSA reading rather than margin status as a surrogate for the quality of oncological resection.

We analysed margin rates comparing nerve sparing and non-nerve sparing cases and performed a separate analysis of T2 and T3 cancer procedures. As expected, procedures on T3 cancers result in a higher proportion of PSM compared to T2 cancers. However even T3 cancers the use of nerve sparing did not result in a higher rate compared to non-nerve sparing procedures. This is possibly related to accurate pre-operative mapping of prostate cancer and surgical planning with nerve sparing being undertaken in cases contralateral to the presumed extracapsular extension of the tumour. If so, this would suggest that a proportion of cancers staged as T3 can still safely undergo nerve sparing prostatectomy depending on the location of the tumour in relation to the NVBs. In practice, a lower proportion of T3 cancers were selected to have a nerve sparing procedure as shown in [Figure 2A](#).

Our review has several limitations. It includes only published results in the English language, all of which are from non-randomised studies (i.e., patients were not randomly allocated to treatments). An absence of RCTs in this area is stark and makes the systematic review timely. The results of the individual studies are subject to various difficulties in interpretation related to their non-randomised nature. These may include selection bias in baseline characteristics, such as age, PSA level and tumour stage, in favour of nerve sparing cases. Surgeon experience, differences in outcome definition and timing of outcome reporting, surgical technique variation, and loss to follow up introduce additional risk of bias.

The absence of RCTs and risk of bias limit the recommendations for clinical practice which can be extrapolated from this review. Performing nerve sparing with same aim of improving continence rates should be considered in impotent patients (particularly as we do not see an increased risk of PSM, even in T3 cancers). The argument for NVB preservation in patients who strongly wish to maintain sexual function after prostate cancer surgery is a stronger one, and nerve sparing can also be performed in T3 cancer patients who have had their cancer accurately staged with adequate imaging and biopsy and tumour location and extent permits a clear margin of resection.

CONCLUSION

This systematic review demonstrates a positive association between nerve sparing and better functional outcomes after prostate cancer surgery. The association with potency is more robust than that for continence outcomes. None of the studies showed evidence that nerve sparing might increase the risk of PSM either for T2 or for T3 cancers. In two studies, the observed proportion of PSM for operations on T3 was in fact lower with nerve sparing. The reason for this is unclear.

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