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Original Article

Impact of frozen section on long-term outcomes in robot-assisted laparoscopic prostatectomy

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Objectives

To compare 1-year functional and 5-year oncological outcomes of men undergoing robot-assisted laparoscopic prostatectomy (RALP) with neurovascular structure-adjacent frozen-section examination (NeuroSAFE) with those in men undergoing RALP without NeuroSAFE (standard of care [SOC]).

Subjects and Methods

Men undergoing RALP in our centre between 1 January 2009 and 30 June 2018 were enrolled from a prospectively maintained database. Patients were excluded if they had undergone preoperative therapy or postoperative adjuvant therapy or were enrolled in clinical trials. Patients were grouped based on use of NeuroSAFE. Follow-up was censored at 5 years. The primary outcome was difference in time to biochemical recurrence (BCR) on multivariable analysis, defined as prostate-specific antigen (PSA) >0.2 ng/L on two consecutive measurements. Secondary outcomes were difference in 1-year erectile dysfunction and incontinence.

Results

In the enrolment period, 1199 consecutive men underwent RALP, of whom 1140 were eligible, including 317 with NeuroSAFE and 823 with SOC. The median PSA follow-up was 60 months in both groups. Rates of 5-year BCR were similar on Kaplan–Meier survival curve analysis (11% vs 11%; $P = 0.9$), as was time to BCR on multivariable Cox proportional hazards modelling (hazard ratio 1.2; $P = 0.6$). Compared with the SOC group at 1 year, the NeuroSAFE group had similar unadjusted rates of incontinence (5.1% vs 7.7%) and lower unadjusted impotence (57% vs 80%). On multivariable analysis, NeuroSAFE patients had equivalent risk of incontinence (odds ratio [OR] 0.59, 95% CI 0.17–1.6; $P = 0.4$) but significantly reduced risk of erectile dysfunction (OR 0.37, 95% CI 0.22–0.60; $P < 0.001$).

Conclusions

For men undergoing RALP, compared with SOC, NeuroSAFE patients had equivalent time to BCR and risk of 1-year incontinence, and significantly lower risk of 1-year erectile dysfunction.

Keywords

biochemical recurrence, frozen section, prostate cancer, robot, prostatectomy

Introduction

For men with localised prostate cancer who undergo surgery, robot-assisted laparoscopic prostatectomy (RALP) has become the 'gold standard' approach, chosen for 84% of men in the United States [1] and 92% in the United Kingdom [2]. The key oncological outcome is biochemical recurrence (BCR). Functional outcomes are also vital, and preservation of the prostate neurovascular bundles is associated with superior continence and potency [3]. However, tumour may be present in nerve bundles, therefore, nerve-sparing surgery increases the risk of positive surgical margins (PSMs) [4], which are associated with a 20% increase in 5-year BCR rates [5].

The degree of dissection of the neurovascular bundle has therefore traditionally been important when considering between lower BCR or superior potency [4]. The surgeon must balance these competing demands when choosing the degree of neurovascular bundle dissection. Typically, this decision was based solely on preoperative information on

clinical tumour stage from rectal examination and MRI, biopsy Gleason grade and nomograms. These were frequently inaccurate [6]. Subsequently, RALP patients commonly received either unnecessary excision of neurovascular bundles for wholly intraprostatic tumours, or high rates of PSMs when nerve sparing was performed [4,7].

Neurovascular structure-adjacent frozen-section examination (NeuroSAFE) offers the oncologically safe option of microscopically individualised dissection. Developed by the Martini Clinic, Germany, this approach involves RALP with one or both neurovascular bundles initially left intact [8]. The prostate specimen is removed, painted to indicate the surfaces adjacent to each neurovascular bundle and sent for rapid intra-operative frozen section of just those posterolateral neurovascular structure-adjacent areas. Patients with a positive result on frozen section undergo additional resection of the relevant neurovascular bundle(s). The aim is maximum preservation of the neurovascular bundles with subsequently optimised potency and continence, without compromising tumour resection. This technique is now widely used, with uptake in the United States [9–11], the United Kingdom [12], the Netherlands [13], Italy [14], Turkey [15] and South Korea [16]. We commenced use in 2012 [17–19]. However, success has generally been measured in rates of PSMs and nerve sparing, which are indirect intra-operative correlates of the long-term outcomes relevant to patients, namely, BCR, continence and potency.

To date, only one study has reported the impact of NeuroSAFE vs standard of care (SOC) on 1-year functional outcomes [12] and only one has reported its impact on 5-year BCR rates [8]. None has simultaneously assessed the ability to improve potency while maintaining long-term oncological safety. This study aimed to compare 1-year functional and 5-year oncological outcomes in men undergoing RALP with and without NeuroSAFE use. We hypothesise that, compared with SOC, NeuroSAFE patients will have equivalent BCR and continence, and potency will differ.

Subjects and Methods

Men undergoing RALP in our centre during the period 1 January 2009 and 30 June 2018 were identified from a prospectively maintained database. Patients were excluded if they had received preoperative treatment, such as hormonal or radiation therapy, or postoperative adjuvant radiotherapy therapies, or if they were enrolled in clinical trials [20]. Patients were grouped based on use of NeuroSAFE or not (SOC). The decision to use NeuroSAFE was based on surgeon and patient preference, taking into account preoperative potency and oncological data (PSA, biopsy Gleason grade, tumour characteristics on MRI) and intra-operative findings. The procedures were performed by four surgeons. All had performed >200 RARPs with SOC before commencing use of NeuroSAFE. The study period included the commencement and learning curve of all surgeons and histopathologists with NeuroSAFE. NeuroSAFE use reached approximately 50% of patients in 2016 and has since remained at this proportion. Depending on surgeon preference, in cases of positive margin on frozen section, the entire ipsilateral neurovascular bundle was taken either in all cases or when positive margin length was >1 mm. All patients were routinely prescribed penile rehabilitation with tadalafil 20 mg twice per week, commencing after removal of the urinary catheter and consultation with a urology nurse practitioner. Per patient preference, men unable to achieve erections adequate for intercourse spontaneously were then offered either a longer period of rehabilitation/observation or progressively more invasive options, starting with on-demand higher dose phosphodiesterase-5 inhibitors (sildenafil 100 mg).

The primary outcome was time to BCR. Time was measured between the date of surgery and the date of BCR or censor. BCR was defined as two consecutive PSA values >0.2 ng/L [21]. Secondary outcomes were continence and potency 1 year postoperatively.

The PSA data were obtained from hospital electronic pathology records. One-year functional outcomes were obtained from outpatient clinic letters. Both continence and potency were assessed on previously reported four-item scales [19]. For continence, this was pad free (0), safety pad but minimally wet (1), 2–3 pads/day (2) and ≥4 pads/day (3). Scores 0–1 were considered to represent continence. Postoperative potency was defined as erections adequate for penetrative intercourse occurring spontaneously (0), with oral medications (1), intra-cavernosal injection (2) or inadequately (3). Scores 0–1 were considered to represent potency.

Statistical Analyses

Patient pooled demographic data and outcome data were presented qualitatively in tables. Continuous data, such as age, were summarised as medians with interquartile range and compared between groups using the Kruskal–Wallis/Mann–Whitney *U*-test. Categorical measures, such as proportion with European Association of Urology (EAU) high-risk disease, were summarised as proportions and assessed with Pearson's chi-squared test. All tests were two-tailed. Significance for the primary outcome was assessed at the 5% alpha level. Analysis was conducted in R [22].

Multivariable analysis of time to BCR was performed using Cox proportional hazards modelling and displayed as a Kaplan–Meier survival curve. Data used in multivariable analyses for BCR included preoperative factors (age, PSA, biopsy Gleason score, clinical stage, EAU risk group) and histological factors (surgical margin status and pathological

tumour and nodal stage). Data used for multivariable analyses of functional outcomes were age, American Society of Anaesthesiology score and preoperative erectile function.

Ethics

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of the National Health Service Health Research Authority (23/PR/1210).

Results

During the enrolment period, 1199 consecutive patients underwent RALP at our centre, including 331 with and 868 without NeuroSAFE. Patients were excluded due to preoperative therapies (one patient), postoperative adjuvant therapies (46), or enrolment in the RADICALS trial (12). The ratio of excluded patients was equivalent in the NeuroSAFE and SOC groups (P = 0.5). Subsequently, 1140 eligible patients were analysed. Cohort data are presented in Table 1. The median PSA follow-up was 60 months in both groups, with interquartile ranges of 24–60 and 33–60 months in the NeuroSAFE and SOC groups, respectively. Compared with SOC, patients receiving NeuroSAFE were equivalent in biopsy Gleason grade, clinical tumour stage, positive node status and surgical margin status. However, they were significantly younger (median age 60 vs 65 years), had lower preoperative PSA level (6.5 vs 7.4 ng/L), were more frequently classified as high risk using the EAU stratification (45% vs 34%) and more likely to have private health insurance (27% vs 7%).

Table 1 Patient data by cohort.

	NeuroSAFE	Standard of care	*P* value
Initial number of patients	331	868	
Excluded, *n* (%)	14 (4)	45 (5)	0.49
Preoperative data			
Eligible patients	317	823	
Age, median, years	59.9	64.7	**<0.00001**
PSA, median, ng/L	6.5	7.4	**<0.00001**
Biopsy Gleason Grade Group, *n*			
1	107	298	0.6
2	153	363	
3	34	110	
4	21	47	
5	2	5	
Clinical tumour stage, median	T2b	T2a	**<0.00001**
Proportion with EAU high risk, *n* (%)	143 (45)	279 (34)	**0.0004**
Potent, *n* (%)	289 (91)	600 (73)	**<0.00001**
Privately insured, *n* (%)	85 (27)	59 (7)	**<0.00001**
Postoperative data			
Pathological tumour stage, *n*			
pT0	0	3	0.052
pT2	259	623	
pT3	58	195	
pT4	0	2	
Pathological lymph node metastasis (pN+), *n* (%)	1 (0.3)	9 (1.1)	0.21
Positive surgical margins, *n* (%)	59 (19)	134 (16)	0.9

Statistically significant univariable results in bold. EAU, European Association of Urology; NeuroSAFE, neurovascular structure-adjacent frozen-section examination.

Primary Outcome

On univariable analysis, BCR incidence was similar in the SOC (78 events) and NeuroSAFE cohorts (36 events). The Kaplan–Meier survival curve estimated BCR rates at 5 years to be equivalent at 11% in the NeuroSAFE group and 11% in the SOC group (P = 0.91 log rank test; Fig. 1). On multivariable analysis, compared with SOC, time to BCR amongst the NeuroSAFE group was not significantly increased (hazard ratio [HR] 1.2, 95% CI 0.69–2.0; P = 0.6). Factors that were associated with increased risk of BCR were higher PSA level (per 10-unit increase, HR 1.0, 95% CI 1.0–1.1; P = 0.04), higher Gleason grade (Group 1 vs. Group 5: HR 11, 95% CI 2.5–44; P = 0.001), positive pathological node status (HR 7.4, 95% CI 2.5–22; P < 0.001) and positive

Fig. 1 Kaplan–Meier survival curve comparing biochemical recurrence by group. NeuroSAFE, neurovascular structure-adjacent frozen-section examination; SoC, standard of care.

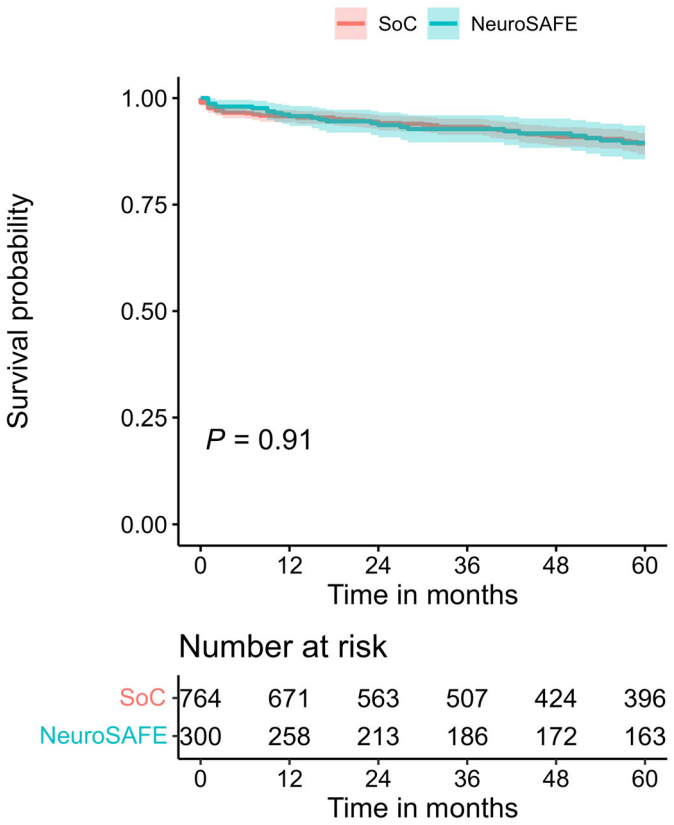


Table 2 Multivariable analysis of factors associated with time to biochemical recurrence.

	N (%)	HR (multivariable) HR (95% CI; *P* value)
NeuroSAFE		
0	823 (72)	–
1	317 (28)	1.16 (0.69–1.95; $P = 0.6$)
Age (years)		
Mean (SD)	62.8 (6.6)	1.00 per 10 year increase (0.99–1.02; $P = 0.4$)
PSA (ng/L)		
Mean (SD)	8.5 (5.8)	1.02 per 10 μg/L increase (1.00–1.05; $P = 0.070$)
Gleason grade		
1	405 (36)	–
2	516 (45)	1.82 (0.79–4.21; $P = 0.163$)
3	144 (13)	3.38 (1.37–8.37; $P = 0.008$)
4	68 (6.0)	5.63 (2.19–14.46; $P < 0.001$)
5	7 (0.6)	10.63 (2.54–44.37; ***P* = 0.001**)
Clinical T stage		
1	337 (30)	–
2	718 (63)	0.96 (0.49–1.86; $P = 0.9$)
3–4	77 (6.8)	1.16 (0.46–2.92; $P = 0.8$)
EAU risk group		
Low	232 (20)	–
Intermediate	484 (43)	0.75 (0.23–2.39; $P = 0.623$)
High	422 (37)	1.24 (0.37–4.19; $P = 0.730$)
Insurance status		
Public	996 (87)	–
Private	144 (13)	0.59 (0.30–1.16; $P = 0.13$)
pT stage		
0–1	11 (1.0)	–
2	874 (77)	0.21 (0.03–1.65; $P = 0.14$)
3–4	255 (22)	0.54 (0.06–4.48; $P = 0.6$)
Node status		
0	1118 (99)	–
1	10 (0.9)	7.43 (2.47–22.39; ***P* < 0.001**)
Margin status		
0	947 (83)	–
1	193 (17)	1.94 (1.19–3.16; ***P* = 0.008**)

Statistically significant multivariable results in bold. %, proportion; CI, confidence interval; EAU, European Association of Urology; HR, hazard ratio; Intermed, intermediate; N, number; NeuroSAFE, neurovascular structure-adjacent frozen-section examination.

surgical margin status (HR 1.9, 95% CI 1.2–3.2; $P = 0.008$ [Table 2]).

Secondary Outcomes

At 1 year postoperatively, incontinence was reported by 13 (5.1%) and 44 (7.7%) men in the NeuroSAFE and SOC groups, respectively. Continence data were missing for 60 (19%) NeuroSAFE and 252 (31%) SOC patients. On multivariable analyses, only older age was associated with increased risk of incontinence (odds ratio [OR] 1.1, 95% CI 1.0–1.1; $P = 0.005$). Compared with SOC, incontinence was equivalent in the NeuroSAFE group (OR 0.59, 95% CI 0.17–1.6; $P = 0.4$ [Appendix S1]).

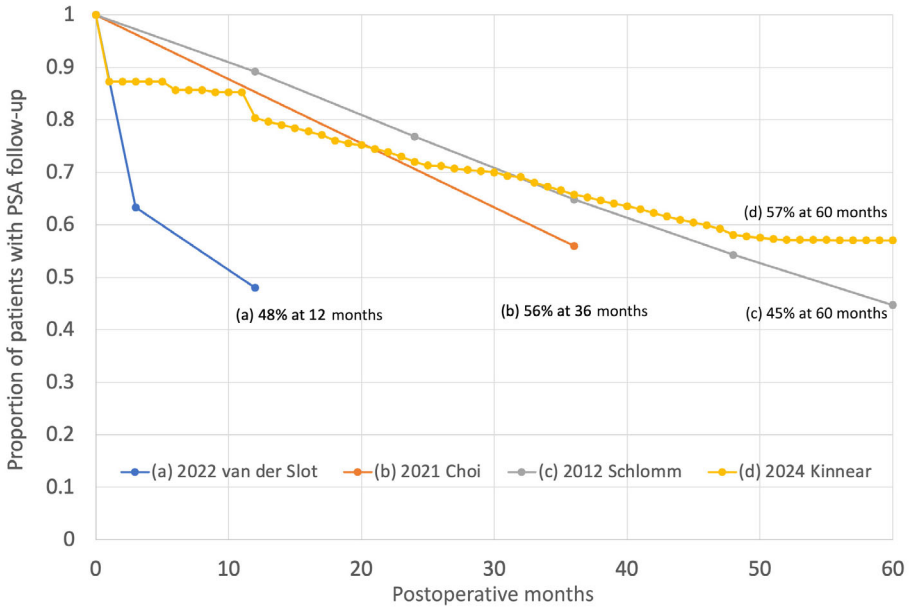
At the same time point, impotence was reported by 145 (57%) and 436 (80%) men in the NeuroSAFE and SOC groups, respectively. One-year potency data were missing for 64 (20%) NeuroSAFE and 277 (34%) SOC patients. On multivariable analyses, older age (OR 1.1, 95% CI 1.0–1.1; $P = 0.001$) and preoperative erectile dysfunction (OR 5.8, 95% CI 3.1–12; $P < 0.001$) were associated with increased risk of impotence. Compared with SOC, risk of impotence was significantly lower in the NeuroSAFE group (OR 0.37, 95% CI 0.22–0.60; $P < 0.001$ [Appendix S2]).

Discussion

In a single-centre cohort in the United Kingdom, this study enrolling >1000 consecutive patients undergoing RALP found that, compared with SOC, NeuroSAFE patients had equivalent time to BCR and risk of 1-year incontinence, and significantly lower risk of 1-year erectile dysfunction. The NeuroSAFE approach relies on the central tenet that more aggressive dissection, with greater sparing of the neurovascular bundle but also potential greater risk of leaving residual tumour, can be safely mitigated by intra-operative frozen section, leading to improved potency outcomes without compromising long-term oncological outcomes. These findings represent the most significant validation to date of this principle. This should encourage urologists to consider commencing intra-operative frozen section in their practice, to improve postoperative potency for their patients.

This is the first study to present both functional and long-term (≥5 year) oncological data for this technique, and only the second study to report 5-year BCR data at all. The first, conducted at the Martini Klinik, Germany, was similarly a single-centre retrospective cohort study [8]. In that study, Schlomm et al. reported 54% of patients were lost to follow-up, and of the remainder, 5-year BCR-free survival was similar in the SOC and NeuroSAFE groups (75% vs 74%; $P > 0.05$) on Cox regression multivariable analysis. Two other NeuroSAFE studies have reported both BCR and loss to follow-up data (Fig. 2). In the Netherlands, van der Slot et al. reported a cohort of RALP patients, in which, after a median of 12 months, 52% of patients were lost to follow-up and BCR was observed in 25% and 13% of the SOC and NeuroSAFE groups, respectively [13]. In contrast to the NeuroSAFE approach of intra-operative microscopic assessment of the posterolateral (nerve-bundle-adjacent) surfaces of the prostate, Choi et al. reported the outcomes of South Korean patients undergoing RALP with frozen sections of periurethral tissue, bladder neck, and dorsal vein [16]. After 36 months, 44% of patients were lost to follow-up, and the 3-year BCR-free survival rate was 77% in the frozen section group, with no SOC comparator group available. Compared with these publications, the present study had a lower proportion of patients lost to follow-up after 5 years (488; 43%) and a BCR incidence of 10%–11% in both groups. This robust long-term patient retention allows certainty regarding the excellent oncological results.

Fig. 2 Comparison of proportion of patients with PSA follow-up in NeuroSAFE studies reporting biochemical recurrence. NeuroSAFE, neurovascular structure-adjacent frozen-section examination.



An additional benefit of the NeuroSAFE technique is that a greater proportion of men may be eligible for surgery, as the availability of immediate histological analysis and re-resection supports surgery in high-risk disease. European and Asian studies indicate that, amongst men with localised prostate cancer, 35% will have high-risk disease [23,24]. However, radiotherapy is often favoured in these men, therefore, high-risk patients typically comprise only 12%–16% of RALP cohorts [25,26]. When these high-risk patients receive RALP, typically only 3% receive bilateral nerve sparing [27]. In this study, 45% of patients in the NeuroSAFE group had high-risk disease, of whom 86/143 (60%) initially received bilateral nerve sparing (with uni- or bilateral neurovascular bundle resection post-frozen section necessary in 13 men).

Another detriment of NeuroSAFE is the cost of laboratory staff labour and materials, and extended operating time (approximately 20–30 min per case). This has been mentioned by previous authors [9,13,16]. Our department believes that these are justified by the superior functional outcomes delivered to patients. Additionally, NeuroSAFE only involves microscopic examination of the two postero-lateral surfaces of the prostate. Positive margins at other sites will not be detected.

This study is limited by its non-randomised nature, with the use of NeuroSAFE based on surgeon/ patient preference leading to potential selection bias. However, the authors believe this was mitigated by the multivariate analyses, which included preoperative oncological and functional factors. Additionally, whilst long-term follow-up was higher than all previous NeuroSAFE works (Fig. 1), a moderately large proportion (43%) of patients remained lost to follow-up after 5 years and overall survival data were also unavailable. Furthermore, 59 patients (5%) were excluded because they had received adjuvant therapy for a variety of reasons, which included pathological tumour stage pT3-4, PSM, or PSA rising but not yet reaching 0.2 μg/L. It is probable that, without these treatments (typically external beam radiotherapy and androgen deprivation therapy), some of these patients would have reached the criteria for BCR.

In conclusion, for men undergoing RALP, compared with SOC, NeuroSAFE patients had equivalent time to BCR and risk of 1-year incontinence, and significantly lower risk of 1-year erectile dysfunction. Urologists should consider incorporating NeuroSAFE into their practice to improve potency. Future research in the form of cost–benefit analysis of this technique is required.

Disclosure of Interest

None.

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Author Contributions

NK created the concept. NK, PCF, CO, SA, OH and AJ performed data collection. MO'C performed the statistical analyses. NK obtained ethics approval and wrote the first manuscript. SA, TL, NV and JA provided supervision. All authors refined the final manuscript and agreed to be accountable for all aspects of the work.

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Abbreviations: BCR, biochemical recurrence; EAU, European Association of Urology; HR, hazard ratio; NeuroSAFE, neurovascular structure-adjacent frozen-section examination; OR, odds ratio; PSM, positive surgical margin; RALP, robot-assisted laparoscopic prostatectomy; SOC, standard of care.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Multivariable analyses of association between 1-year continence and selected factors.

Appendix S2. Multivariable analyses of association between 1-year erectile function and selected factors.