NeuroSAFE PROOF Feasibility Study: brief report of peri-operative outcomes, histological concordance and feasibility.

Eoin Dinneen[1], Aiman Haider[2], Alex Freeman[2], Jonathan Oxley[3], Tim Briggs[4], Senthil Nathan[4], John Kelly[1,4], Jack Grierson[1], Raj Persad[5], Jon Aning[5], Neil Oakley[6], Imran Ahmad[7], Lorenzo Dutto[7], Greg Shaw[1,4].

Author Affiliations

1. Division of Surgery and Interventional Science, University College London, Charles Bell House, 43-45 Foley Street, Fitzrovia, London, W1W 7TS, UK.
2. University College Hospitals London, Department of Histopathology, 60 Whitfield Street, London, W1T 4EU
3. North Bristol Hospitals Trust, Department of Histopathology, Southmead Hospital, Southmead Lane, Westbury-on-Trym, Bristol, BS10 5NB.
4. University College Hospitals London, Department of Urology, Westmoreland Street Hospital, 16-18 Westmoreland Street, London, W1G 8PH.
5. North Bristol Hospitals Trust, Department of Urology, Southmead Hospital, Southmead Lane, Westbury-on-Trym, Bristol, BS10 5NB.
6. Sheffield Teaching Hospitals NHS Foundation Trust, Department of Urology, Royal Hallamshire Hospital, Sheffield, S10 2JF.
7. Glasgow & Clyde NHS Trust, Department of Urology, Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow G51 4TF.

Corresponding Author

Mr Eoin Dinneen BA (Hons), MB ChB, MPhil, MRCS.

eoin.dinneen@nhs.net

Word Count: 509

Author email addresses (in the order they appear on authorship list):

aiman.haider@nhs.net, alex.freeman2@nhs.net, Jon.Oxley@nbt.nhs.uk, tim.briggs@nhs.net, s.nathan@nhs.net, j.grierson@ucl.ac.uk, Raj.Persad@nbt.nhs.uk, Jonathan.Aning@nbt.nhs.uk, Neil.Oakley@sth.nhs.uk, Imran.Ahmad@glasgow.ac.uk, Lorenzo.Dutto@ggc.scot.nhs.uk, gregshaw@doctors.net.uk .

Erectile dysfunction is a common and significant side effect of radical prostatectomy (RP). Nerve-sparing (NS) RP improves recovery of erectile function, but the quality of NS can be impaired by concern about the oncological risks of positive surgical margins (PSM). The NeuroSAFE technique is an approach that uses intraoperative frozen section (IFS) analysis of the posterolateral neurovascular structure adjacent to the prostate margin to promote optimal NS and reduce the risk of PSM during RP (1). The NeuroSAFE PROOF feasibility study (NCT03317990; regional ethics committee reference 17/LO/1978) is the first randomised controlled trial (RCT) of IFS during RP. This pragmatic, multicentre trial compared robot-assisted RP (RARP) with and without the NeuroSAFE technique (2). Here we report perioperative outcomes and histological concordance from the feasibility study.

Forty-nine men underwent RARP at two UK NHS participating centres (UCLH and North Bristol Trust) from 29th May 2018 until 25th March 2019. Twenty-five men underwent NeuroSAFE RARP and 24 men underwent standard RARP as per randomisation (see Table 1 for clinical and pathological characteristics).

Concordance assessment was performed between frozen section and final section of the 50 neurovascular structure adjacent margins (2 per patient) submitted in the NeuroSAFE arm. Frozen section had a sensitivity of 100%, specificity 92.7%, PPV 75% and NPV 100% (Fisher's Exact test *P* <.0001). The ROC curve is demonstrated in (see Supplementary Material) with an area under the curve (AUC) of 0.963 (95% CI 0.914 to 1, p = <0.001).

Detailed operation duration data was collected prospectively for all RARP procedures in both arms. The mean length of NeuroSAFE RARP was 3 hours 16 minutes (95% CI 3 hrs 2 mins to 3 hrs 30 mins) versus 2 hours 13 minutes (2 hrs 2 mins to 2 hours 25 mins, *P*=<0.0001) in the control arm (see Table 1). Given the extra time and personnel involved in performing the NeuroSAFE technique, the additional cost of the procedure was estimated at £1,000. There were no Clavien-Dindo complications >2 recorded in either arm. There was no morbidity associated with the additional time under general anaesthesia in the NeuroSAFE arm.

Recent guidelines on performance of NS in RP suggest that IFS can be beneficial, but this recommendation is made without level 1 evidence(3, 4). Conversely, many authors point out that widespread dissemination of the NeuroSAFE technique is limited by the extra expense and organizational requirements necessary to perform IFS(5). The NeuroSAFE PROOF Feasibility Study confirms the additional cost of the NeuroSAFE technique, but it also demonstrates that it is feasible in the UK national healthcare setting and is not associate with short-term adverse outcomes for the patient. These observations are confirmed by the fact that the full NeuroSAFE PROOF RCT is open and recruiting at four UK hospitals (NCT03317990). We hope that our full trial comes at an appropriate time to evaluate what has long been a promising technique to improve outcomes for men undergoing RP, but where there has been a lack of robust evidence. We have proven feasibility and now we are including long-term functional and oncological outcomes in our definitive study. We look forward to keeping your journal and the wider urological community informed of our findings.

1. Schlomm T, Tennstedt P, Huxhold C, Steuber T, Salomon G, Michl U, et al. Neurovascular structure-adjacent frozen-section examination (NeuroSAFE) increases nerve-sparing frequency and reduces positive surgical margins in open and robot-assisted laparoscopic radical prostatectomy: experience after 11,069 consecutive patients. Eur Urol. 2012;62(2):333-40.
2. Dinneen E, Haider A, Allen C, Freeman A, Briggs T, Nathan S, et al. NeuroSAFE robot-assisted laparoscopic prostatectomy versus standard robot-assisted laparoscopic prostatectomy for men with localised prostate cancer (NeuroSAFE PROOF): protocol for a randomised controlled feasibility study. BMJ Open. 2019;9(6):e028132.
3. Mottet N, van den Bergh R.C.N., Briers E, et al. EAU Guidelines. 2019.
4. Dinneen EP, Van Der Slot M, Adasonla K, Tan J, Grierson J, Haider A, et al. Intraoperative Frozen Section for Margin Evaluation During Radical Prostatectomy: A Systematic Review. Eur Urol Focus. 2019.
5. Sighinolfi MC, Eissa A, Spandri V, Puliatti S, Micali S, Reggiani Bonetti L, et al. Positive surgical margin during radical prostatectomy: overview of sampling methods for frozen sections and techniques for the secondary resection of the neurovascular bundles. BJU Int. 2020.

Table 1. Clinical and pathological characteristics of the NeuroSAFE (intervention) and standard (control) arms.

Variable		NeuroSAFE	Standard	*P*
Number of patients		25	24	
Age, years, median (range)		57 (51-66)	55.9 (44-63)	0.66
Mean preoperative PSA (ng/ML) (range)		10.4 (1.2-39.2)	9.5 (4-35)	0.99
Biopsy ISUP (%)				0.5
	1	1 (4)	3 (13)	
	2	19 (76)	17 (70)	
	3	5 (20)	3 (13)	
	4	0	1 (4)	
	5	0	0	
Prostate weight (g) mean (SD)		43.9 (11.9)	42.2 (10.6)	0.712
Path Stage (%)				0.25
	2a/2b	2 (8)	0	
	2c	13 (52)	16 (67)	
	3a	7 (28)	8 (33)	
	3b	3 (13)	0	
Mean tumour volume (mls) (range)		5.0 (0.25-22.27)	4.7 (0.7-12.89)	0.171
Final ISUP (%)				0
	1	2 (8)	0	
	2	17 (68)	21 (83)	
	3	5 (20)	3 (13)	
	4	0	0	
	5	1 (4)	0	
Operation length (hrs: mins) (SD)*		3:16 (31mins)	2:13 (27mins)	<0.0001
CD Complications >2		0	0	

NB. Missing data on 2 cases, both in NeuroSAFE arm. CD = Clavien-Dindo.