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External Validation of the NeuroSAFE Approach to Nerve Sparing in Robotic Assisted Radical Prostatectomy in a British Setting – A Prospective Observational Comparative Study

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INTRODUCTION

Despite improved understanding and technical advancements, nerve sparing prostatectomy has often been compromised in an attempt to ensure a negative surgical margin.

Current strategies including imaging, pre-operative DRE and biopsy information are poor in predicting neurovascular cancer involvement.

Intraoperative frozen section analysis of the excised prostate specimen during a radical prostatectomy has the potential to address these issues.

The Martini-Klinik in Hamburg, Germany developed the intraoperative neurovascular structure-adjacent frozen section examination (NeuroSAFE) technique which has since been internally validated by their group [1, 2].

They reported an increase in nerve spare from 81 % to 97% and a decrease in positive margin rates from 22% to 15% across all stages.

The Hertfordshire and South Bedfordshire Urological Cancer Centre at the Lister Hospital, Stevenage adopted the NeuroSAFE technique in November 2012.

AIM

To externally validate the NeuroSAFE technique in a British setting in men undergoing Robotically Assisted Laparoscopic Prostatectomy (RALP).

METHOD

- We retrospectively analysed our prospectively maintained database of patients who underwent RALP between Nov 2008 and Feb 2017.
- We examined preoperative pathological and functional parameters, intra-operative nerve sparing, post-operative histology as well as functional and oncological follow-up.
- Comparison was made between those who had a NeuroSAFE approach and those who had nerve sparing without NeuroSAFE.
- We also compared all the RALPs before and after the introduction of NeuroSAFE.
- Statistical analysis was done using the two tailed T-test and Chi-Squared analysis.
- We have previously published our technique for RALP and intra-operative frozen section analysis [3]

RESULTS

- 965 men underwent RALP in the time period
- Mature data was available for one surgeon who performed 417 RALPs including 120 NeuroSAFEs.
- The NeuroSAFE cohort had a greater proportion of D'Amico high risk disease (30.8% vs 9.6%, p<0.0001), higher Gleason scores and higher pT stage compared to the non-NeuroSAFE nerve spares.
- Post introduction of NeuroSAFE, more preoperatively potent men underwent bilateral nerve sparing with pT2 disease (84.6% vs. 66.3%, p=0.002) and more overall nerve spares were performed in patients with pT3 disease (65.1% vs 36.7%, p=0.012).
- Overall positive surgical margin rates (PSMR) were lower in the NeuroSAFE cohort compared to those who had nerve sparing without NeuroSAFE (9.2% vs 17.8%, p=0.04).
- 12-months potency rates were higher in the NeuroSAFE cohort for both bilateral (77.3% vs 50.9% p=0.009) and unilateral (70.6% vs 40%, p=0.04) nerve spares.
- Pad-free continence was higher in the NeuroSAFE group (85.7% vs 70.9%, p=0.019), but there was no significant difference between those who were wearing 1 safety pad or less.
- Although we only had short term oncological follow-up, it did not significantly differ between the two groups.

Oncological and Functional outcomes of NeuroSAFE vs. Non-NeuroSAFE nerve spares
** Continent = no pads or 1 precautionary "safety" pad at 12 months or greater follow-up*
† Potent = erections sufficient for intercourse with/without PDE-5 inhibitors at 12 months or greater follow-up

	Non-NeuroSAFE	NeuroSAFE	p value
Overall positive margins	28/157 (**17.8%**)	11/120 (**9.2%**)	**0.040**
T2 positive margins	21/140 (15%)	7/92 (7.6%)	0.09
T3 positive margins	7/17 (41.2%)	4/28 (14.3%)	0.042
BCR	3 (1.9%)	2 (1.7%)	0.88
Salvage XRT	3 (1.9%)	2 (1.7%)	0.88
Adjuvant XRT	3 (1.9%)	7 (5.8%)	0.083
Continence			
Continent*	116/127 (91.3%)	66/70 (94.3%)	0.46
NO pads	90 (70.9%)	60 (85.7%)	0.019
Potency			
Bilateral NS	98 (70%)	72 (67.3%)	0.65
Potent †	28/55 (**50.9%**)	34/44 (**77.3%**)	**0.007**
Potent without PDE-5i	15 (27.3%)	21 (47.7%)	0.036
Unilateral NS	42 (30%)	33 (30.8%	0.89
Potent	12/30 (**40%**)	12/17 (**70.6%**)	**0.044**
Potent without PDE-5i	3 (10%)	3 (17.6%)	0.48

Baseline characteristics of NeuroSAFE and non-NeuroSAFE nerve sparing cohorts

	Non-NeuroSAFE (N=157)	NeuroSAFE (N=120)	p value
Median age	62	58	0.003
Mean pre-op PSA	7.37	7.23	0.78
Biopsy Gleason			
6 or less	87 (55.4%)	37 (30.8%)	<0.0001
3+4=7	54 (35%)	55 (45%)	0.09
4+3=7	10 (6.4%)	17 (14.2%)	0.030
8 or greater	4 (2.5%)	10 (8.3%)	0.029
D'Amico Risk			
Low	63 (40.1%)	21 (17.5%)	<0.0001
Intermediate	74 (47.1%)	59 (49.2%)	0.74
High	15 (**9.6%**)	37 (**30.8%**)	**<0.0001**
pT Stage			
T2	140 (89.2%)	92 (76.7%)	0.005
T3	17 (10.8%)	28 (23.3%)	0.005

Proportion of pre-operatively potent men being offered nerve sparing RALP

	Before 1st NeuroSAFE	After 1st NeuroSAFE	p value
N RALPs in potent men	145	193	
pT2	115 (79.3%)	150 (77.7%)	0.73
Overall Nerve Spare	89 (77.4%)	117 (78%)	0.82
Bilateral	59 (**66.3%**)	99 (**84.6%**)	**0.002**
Unilateral	30 (33.7%)	18 (15.4%)	0.002
Wide Excision	26 (22.6%)	32 (21.3%)	0.82
pT3	30 (20.7%)	43 (22.3%)	0.73
Overall	11 (**36.7%**)	28 (**65.1%**)	**0.012**
Bilateral	4 (36.4%)	8 (28.6%)	0.64
Unilateral	7 (63.6%)	20 (71.4%)	0.64
Wide Excision	19 (63.3%)	14 (32.6%)	0.012

Diagnostic accuracy of NeuroSAFE:

Total NVBs = 227 (107 bilateral frozen sections, 13 unilateral frozen sections)
Total NVBs excised due to suspicion of tumour at margin = 33 (14.5%)
Total NVBs positive for tumour = 14 (42.4%)

Sensitivity = 82.4%
Specificity = 91%
PPV = 42.4%
NPV = 98.5%

CONCLUSIONS

Adoption of NeuroSAFE allowed us to:

- Offer nerve sparing to more patients with **higher risk** disease
- **Reduce PSMR** and maintain oncological safety
- **Improve potency** for bilateral and unilateral nerve spares at 12 months

Further study is needed to validate the approach across multiple surgeons, centres and confirm its long term oncological safety

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