Neurovascular structure-adjacent frozen-section examination (NeuroSAFE) Robotic Assisted Laparoscopic Radical Prostatectomy: Outcomes from 500 consecutive cases in the UK

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Abstract

Objectives

To report the United Kingdom's largest single centre experience of robotically assisted laparoscopic radical prostatectomies (RALP), using the neurovascular structure -adjacent frozen-section (NeuroSAFE) technique. We describe its' efficacy on histopathological and functional outcomes, to aid units in their early stages of adoption of this technique.

Patients & methods

We prospectively collected data from November 2012 – December 2019 on 520 patients who underwent RALP with NeuroSAFE at our Institution. Exclusion criteria was pre-operative indication to perform an extra-fascial nerve spare or wide local excision prostatectomy, including salvage RALP. Our Institution's database was analysed for false positive frozen section (FS) margins as confirmed on paraffin histopathological analysis; console and FS report time; functional outcomes of potency, continence, surgical margins and biochemical recurrence (BCR).

Results

The median (range) of operative console time of our NeuroSAFE RALPs was 145 (90–300) minutes. The mean time of FS processing to report was 35 minutes. In our cohort, positive FS was seen in 30.7% (160/520) of patients, with a confirmatory paraffin analysis in 91.8% of cases (147/160). The neurovascular bundles (NVBs) that underwent secondary resection, contained tumour in 26.8% (43/160) of cases. 77.5% T2, 22.3% T3 cancer was found on final prostate specimen analysis. Biochemical recurrence (BCR) was 6.7% (35/520), of which FS was positive in 40% (14/35) of those cases. Bilateral nerve spare (NS) RALP was statistically significant for potency, over wide excision

from positive FS. There was insufficient evidence of statistically significant association of urinary incontinence and positive surgical margin rates according to NS or NVB resection.

Conclusion

Our mid to long term results of NeuroSAFE RALP describes acceptable functional outcomes. NeuroSAFE enables intra operative confirmation of the oncologic safety of a NS procedure. Patients with a positive FS on NeuroSAFE can be converted to a negative surgical margin (NSM) by wide resection of the NVB. This spared 1 in 4 men from positive margins posterolaterally in our series. No other technique has been validated to offer intraoperative feedback on the oncologic safety of NS RALP. Limitations are absence of a matched cohort of NS RALP without NeuroSAFE in our centre; three surgeons and three Uro-pathologists performing this technique; and the absence of centralised cancer database to capture all outcomes.

Key words: prostate cancer, robotics, prostatectomy, neurosafe, frozen section, outcomes

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Introduction

Urological Surgeons manage prostate cancer by radical prostatectomy through a robotic, laparoscopic or open approach. The aim in this approach is to optimise pentafecta outcomes as proposed by high volume surgical units[i]. Robotic-assisted laparoscopic radical prostatectomy (RALP) has become a dominant surgical approach for localised prostate cancer treatment with the rapid adoption of this technology. There are 5,582 acquired da Vinci® surgical systems around the world, and along with other emerging platforms. A side effect of manipulation during neve sparing (NS) prostatectomy of neurovascular bundles (NVB) described by Walsh[ii], is post prostatectomy erectile dysfunction. The pioneer of robotic urologic surgery, Professor Menon and his team published their experience of RALP having advantages over open prostatectomy (OP) with a faster recovery of potency[iii]. Despite these advances, patients' return of erectile function and sexual intercourse is still variable, ranging from 15% to 87%[iv,v,vi,vii] .

In 2007, the Martini-Clinic Prostate Cancer Centre in Hamburg, Germany conceptualised a technique to enhance NS prostatectomy. A frozen section guided retropubic radical prostatectomy (RRP) approach utilising a whole neurovascular structure–adjacent frozen section examination (NeuroSAFE) was developed. It demonstrated validity to enhance NS ability with the accompanying decrease in positive surgical margin (PSM) rates[viii]. NVB preservation at the Martini-Clinic was now performed with the reassurance given to both surgeon and patient that cancer cells were not left at the resection margin of the prostate specimen. When the frozen section (FS) analysis reported cancer at the margin/s, resection of the relevant NVB would ensure a negative surgical margin (NSM) was achieved.

Since 2008, our institution exclusively performs robotic surgery for localised prostate cancer. The senior author (JA) introduced Martini-Clinic's method to our Institution in 2012. Currently in the United Kingdom, this is the largest single centre series of NeuroSAFE RALPs. As of 2019, more than 500 cases were performed, therefore our aim is to describe the lessons learned. The data is intended to be a reference to units adopting this technique.

Patients and methods

Study population:

Over a 7 year period from November 2012 – December 2019, 520 patients underwent RARP with NeuroSAFE at our Institution, utilising the da Vinci® surgical system. The procedures included in this study were those performed and/or supervised by three surgeons (TL, NV, JA) along with three uro-pathologists (RS, SA and AN) analysing the FS specimens. All data was prospectively collected and maintained in our Institution's registered database. Baseline parameters included age, pre operative PSA, gleason score, number of involved cores, cT stage and ability to have penetrative intercourse or not. Intra and post operative details collected were total and console operative time, blood loss, complications as classified by the Clavien–Dindo system, prostate specimen pathology (gleason score, margin status, TNM stage, and specimen weight), postoperative PSA levels, adjuvant/salvage treatment, as well as post prostatectomy continence and erectile function.

According to D'Amico classification, low and intermediate risk patients were offered a NeuroSAFE RALP if pre-operatively potent. Erectile dysfunction was not an exclusion criteria in this cohort. Patients under D'Amico classification of high-risk were included if a pre-operative MRI prostate stage was < or = T3a and it was oncologically appropriate to perform a unilateral or bilateral nerve spare. Patients with a preoperative clinical or radiological stage > or =T3b disease were not offered NeuroSAFE and hence not included in this study.

NeuroSAFE RALP technique

After induction with general anaesthesia and muscle relaxation from an atracurium infusion, a caudal anaesthetic block performed by administration of 40 mls of 0.25% bupivicaine, 150 µg clonidine and 100 µg fentanyl. Bupivacaine 0.5% is infiltrated to the intended port site insertion sub-peritoneally and to the wounds after skin closure.

After establishment of pneumoperitoneum, a 'W' formation port placement and da Vinci Si® surgical robot is docked to the patient, transperitoneal prostatectomy is performed by an anterior approach with antegrade NVB preservation. RALP was performed with an intrafascial or interfascial nerve spare technique depending on tumour location and grade. An intrafascial NS is performed for low volume and/or low risk disease and interfascial NS is performed for high volume and/or high risk

disease. Intermediate category risk patient's has NS according to surgeon's judgement on achieving safe cancer control. The pneumoperitoneal pressure is temporarily increased from 12 to 20 mm Hg to limit dorsal vein complex (DVC) bleeding during its' incision. This complex is oversewn with a 3/0 V-Loc™ barbed unidirectional polyglyconate suture, to then allow maximal urethral length during apical dissection and striated sphincter preservation. Once haemostasis from the NVB is achieved then the specimen is is placed in a 12 mm Endo-Catch™ bag that is inserted via the Surgiquest™ AirSeal port. All robotic instruments are removed and their ports are inserted deeply into the abdomen under vision, to allow them to maintain their position when pneumoperitoneum stops. It is not necessary to undock the patient robotic side cart. The insufflation is temporarily stop, and this allows the specimen to be extracted through an extended supraumbilical/camera port. The primary surgeon prepares and paints the specimen prior to delivery to the uro-pathologist for FS analysis. The AutoSuture™ balloon port is re-inserted, pneumoperitoneum created and RALP re-commences.

To ensure optimal conditions for cryosectioning, posterolateral surgical margin surfaces are painted with different colours (red =right, violet = left). In the pathology department, the specimens are embedded in freezing medium at – 25 C then sectioned into slices of 10 – 20 blocks. Haemotoxylin and eosin (H&E) staining then follows, and the review by uro-pathologist commences. The entire NeuroSAFE procedure requires a maximum time from receiving to reporting of 35 minutes.

In the event of a positive NeuroSAFE result, an ipsilateral NVB is resected and sent separately for paraffin section analysis. The definitive margin status is determined on the whole prostatectomy specimen, including the NeuroSAFE sections. A histologic detection of malignant cells in resected NVB is defined as pT2+.

Definitions

Post-operative potency and continence was scored from 0 - 3 respectively (see Tables 1 and 2). Similar to our previous published practice[ix], we defined continence for patients requiring no pads or one safety pad. Patients defined as potent were having erections capable for penetrative intercourse with or without a phosphodiesterase type 5 (PDE-5) inhibitor. During follow up consultation, these outcomes were captured by the consulting urologist or nurse specialist.

When FS was positive and this was confirmed on paraffin analysis, the ipsilateral resected NVB either:

1. Contained no malignant glands on the lateral edge, and equated to a NSM for the patient.
2. Contained malignant glands on the lateral edge, and equated to a PSM for the patient.

When FS was negative, no ipsilateral NVB was resected. If in the event, the negative FS was later confirmed to contain cancer on paraffin analysis this equated to a PSM and a **false-negative FS**. A definitive surgical margin status was always reported on the entire prostate specimen, inclusive of the FS sample.

Adjuvant treatment refers to initiation of therapeutics before a PSA threshold of 0.2 ng/mL; salvage treatment refers to initiation of therapeutics if biochemical recurrence (BCR) occurs. BCR was defined when a post RALP PSA was >0.2 ng/mL.

Outcomes

We present our overall PSM rates for patients undergoing NeuroSAFE RALP, along with associated oncological outcomes including BCR and adjuvant/salvage treatment.

NeuroSAFE functional outcomes are analysed at the 12-month follow up interval, for potency and continence rates.

Accuracy between frozen section and final histopathology was also performed in order to determine the correlation of both margin assessments.

Results

Patient Characteristics

The data comprised of 520 patients undergoing a NeuroSAFE RALP between 2012 - 2019. Demographic, operative and pathological data are shown in Table 1. The median age (range) of this cohort was 59 years old (39- 76). The median (range) captured for follow up was 12 (1 – 60) months. NeuroSAFE RALP was performed on D'Amico classified risk prostate cancer patients, where 49% of patients fell into a high risk category.

Robotic console median time was 145 minutes, which was the duration of the docking of the d*a Vinci* system, to undocking on completion of the intracorporeal surgery. Blood loss was at a median of 50 mls (range of 0 - 1000mls). Two intraoperative complications were one patient required temporary conversion to standard laparoscopy when da Vinci system malfunctioned for 20 minutes; the other was unrecognised closure of both ureteric orifices, necessitating emergency bilateral nephrostomy insertion. No rectal injuries, however there was one mortality which was after 30 days port surgery due to a caecal rupture. Median prostate specimen volume was 45 mls (range 13 – 182) and indwelling catheter time was 10 days (7 -56). Cystogram pre TWOC was not performed routinely.

Functional Outcomes

Our patients were assessed for potency in 430/520 (82.7%) patients and continence for 438/520 (84.2%) patients. These were analysed according to NeuroSAFE guided bilateral NS, unilateral NS (with contralateral wide excision) or wide excision/both NVB removed. Table 2 demonstrated that potency scores of 0 and 1 were more likely achieved with both NVB spared. This is supported by a statistically significant association from a Kruskal-Wallis test calculation ($p = <0.01$). Table 3 demonstrated insufficient evidence for a statistically significant association with NVB spared and continence rates in our cohort ($p=0.49$)

Oncological and NeuroSAFE Outcomes

PSM were assessed under the categories of NeuroSAFE guided bilateral NS, unilateral NS (with contralateral wide excision) or wide excision bilaterally. These PSM were related to the whole prostate specimen, including the sections examined for FS. As shown in Table 4, there was insufficient evidence to claim that NeuroSAFE affected the PSM rates from RALP ($p=0.98$ from Fisher's exact test). On final pathological staging, T2 was 77.5% and T3 was 22.3%. The BCR rate for our cohort was 6.5% (35/520), which was associated with positive FS in 40% (14/35) and tumour in the resected NVB in 8.6% (3/35).

NeuroSAFE Concordance with Standard Histopathology.

The mean time of extracting the prostate specimen, side specific painting by the surgeon, transportation to uro-pathologist for cryostat processing and reporting was 35 minutes. In our cohort, positive FS was seen in 30.7% (160/520) of patients, with a confirmatory paraffin analysis in 91.8% of patients (147/160). The neurovascular bundles (NVBs) that underwent secondary resection, contained cancer in 26.8% (43/160) of patients.

To purely analyse at microscopic level, a FS analysis for each side of a prostate specimen was performed 839 times (321 bilateral nerve spares and 197 unilateral nerve spare cases). The sensitivity of FS against confirmatory paraffin test was 95.5% for our cohort, the specificity was 98.1% as shown in Table 5. Table 6 summarises the median positive FS margin length to relate it to a PSM on paraffin results.

Discussion

The application of robotic surgery provided the advantages of three-dimensional enhanced visuals with magnification. The wristed instrumentation allows six degrees of surgical movement, coupled with the human advantage of the seventh degree of movement. This has pushed urological surgeons to improve their individual dissection of the nerve containing fascial layers off the prostate to aid in optimising functional outcomes. When confined to do such surgery in a deep android pelvis, then the multiport robot has a clear advantage.

Since we adopted the technique of NeuroSAFE early, our objective was to ensure that it's use in RALP was safe and feasible as a complimentary approach to nerve sparing in patients with prostate cancer. The challenges during our initial introduction and experience at our Institute was uro-pathologist and laboratory co-ordination with surgical team, timely transfer of the specimen, interpretation of frozen section results and the oncological outcome of the decision based on FS. 10-20 FS slides are processed and reported per bilateral NS with the focus of 2 – 3 laboratory technicians and one uropathologist per NeuroSAFE case. Despite instances of deeper levels of FS being necessary if inked margins are incomplete, our average processing to report time of 35 minutes is comparable to previously published studies[x]. Improvement can be made with an increase in dedicated cryostats with regular complete margins, and second opinions from uro-pathologist can be helpful in optimising time efficiency.

As more centres in Europe are adopting this approach, the urological community are anticipating the results of the randomised clinical trial (RCT): NeuroSAFE PROOF[xi]. This RCT is open and as of 2020, 4 UK sites are recruiting with 150 patients randomised. This will NS RALP will impact positively on outcomes of men. The interesting point in the design is the approach to NVB resection will be only full removal form base to apex. This is if FS either contains Gleason 4 or 5, >2mm or multiple section involvement. This is certainly in contrast to practice already mentioned above, but will ensure that inter surgeon variability to positive FS is minimal. A multicentre RCT's benefit is the wide geographic spectrum of patients along with the uptake of this technique by smaller non-academic institutions under guidance of their nearby counterparts. However, the variation in surgeon experience and technical approach is a potential confounder. Specifically in regard to nerve spare approach of antegrade or retrograde, as this will impact on potency recovery[xii]. Urinary continence structure preservation should be considered a variable, whether by Retzius sparing[xiii] or a modified apical dissection[xiv]. The utilisation of the da Vinci Xi or X allows a retrograde nerve spare approach whereas the Si does not camera toggle from the console control panel. In this regard, the model of robotic platform could be considered as a variable, particularly when the single port model (set to become available in Europe) will be introduced and the modifications needed for its use[xv]. The differing uro pathologist's experience and cryostat/pathological laboratory accessibility from the operating room will all impact on the FS process and should be accounted for.

As mentioned above, a criticism of NeuroSAFE will be the non standardised approach to parameters that determine secondary resection of the NVB. Institution's practice on FS reports varies, such as one published practice of a FS <1mm of Gleason pattern 3 being a criteria to not resect the ipsilateral NVB[xvi]. This could be supported as the NVB can be misinterpreted as cancer[xvii] and studies have observed no difference in BCR free survival in PSM of 3mm or less[xviii,xix]. A Department's standardisation of protocols to remove or leave the ipsilateral NVB based on FS: length of tumour at the inked margin, number of slides involved and Gleason pattern should be universally agreed. A inter surgeon variation of protocol with regard to this intraoperative decision-making may introduce an unmeasured bias in our analysis of NeuroSAFE. Table 6 showed average length of tumour art FS in relation to paraffin confirmatory examination: with 6mm likely to be positive and 2.5mm to be negative. Such an agreement should come from all local uro-pathologist and surgeons who are involved in this procedure. However, our concordance with positive and negative FS to paraffin histology has shown improved sensitivity and specificity since our last examination of our experience in 2017[ix].

In our their experience of over 500 procedures, our operative duration was around 145 minutes, in keeping with non NEUROSAFE RALP cases previously published. The added time of FS processing can be utilised by haemostasis, pelvic lymph node dissection, posterior musculofascial layer reconstruction and a vesicourethral anastomosis with or without bladder neck reconstruction. No patients required intraoperative blood transfusion, and this technique should not increase this risk. Our one intra-operative complication was robot temporarily stalling, but this did not interrupt the completion of the case. Comparing to our previous experience, we offer more successful NS, whether bilateral or unilateral, by the reduced conversion to wide excision: 23.8%[ix] in previous publication down to 5.2% (see Table 1). The learning curve and selection criteria for men has aided in the accomplishment of this, but so has surgical experience with decision of intra or interfascial dissection.

Potency from Table 2 reveals that more NVBs spared was favourable for potency recovery, which is in line with what is expected. Our urinary continence, defined as using no pads, was achieved in both grades of NS and complete NVB resection without evidence of a significant difference (Table 3). This might explained by standard bladder neck sparing approach and the technical modifications of sparing or minimising trauma to anterior structures of the urethra[xiv], which is independent but complimentary to the NS approach.

The true success and durability of NeuroSAFE will be the oncological outcomes. PSM rates across all margins were not altered significantly by the use of FS (see Table 4) and this could be down to the fact that bladder neck sparing (BNS) a technique employed by all our Team. A recent systematic review[xx] found no association of BNS with an increase in PSM at the prostate base, however a separate publication found that it does impact on PSM[xxi]. However controversial, both studies agree that continence is seen earlier with BNS as mentioned above. Efforts to preserve urethral complex structures[xiv] has been associated with higher focal PSM which would be in keeping with techniques adopted recently at our Institute. No correlation with positive FS nor any associated resected NVB that contained tumour and the development of BCR. Our BCR cases are referred and/or managed with Radiation Oncology opinion in first instance. This was not captured for our patients as our Cancer site with electronic records is Regional and not integrated into our Surgical site.

Lastly, as experience is gained, successful speed and precision become an unconscious effort, leading to improved patient outcomes. Our Institute is the first Royal College of Surgeons of England training

site for Pre-Consultant grades in Robotic Urologic Surgery. The patients will have outcomes that can be reflective of earlier learning curves, however we have seen that this can be adapted to shortened by modular training and dual consoles[xxii] at minimal expense to pentafecta outcomes. Limitations of this study are lack of centralised NeuroSAFE database that receives outcome data from patients externally referred to us for RALP. Future studies should be aimed at contemporary and matched non NeuroSAFE cohorts, in a single high volume centre with experience in this technique. Future RCT should have protocols to blind surgeon's to NeuroSAFE once prostatectomy is placed in the specimen bag. The hypothesis of whether a NS technical bias is present due to knowledge of a NeuroSAFE case should be limited.

In conclusion, NeuroSAFE RALP is a safe option for treating prostate cancer and optimising NS capability. An initial experience in this approach may be challenging but satisfactory potency results are to be gained. A recognition of secondary NVB resection protocol is key and comparative cost analysis will require further study. A novel confocal microscopy is being assessed but it has no real time validation, but its symbiosis with this technique is apparent[xxiii]. NeuroSAFE oncological safety has now been validated in a British setting.

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Table 1: Clinicopathologic data for NeuroSAFE cohort

	Number / (median)	**% / (range)**
Age	59	(39 – 76)
Preoperative PSA ng/mL	(4)	(0.22 – 37)
D'Amico Classification:		
Low	64	12.3
Intermediate	201	38.7
High	255	49

	Number / (median)	% / (range)
Clinical ≤T2	484	93
Clinical T3a	36	7
Biopsy Gleason Score*		
Gleason 3+3	160	30.6
Gleason 3+4	271	52.1
Gleason 4+3	59	11.3
Gleason >8	29	5.6
Console time in minutes	(145)	(90 – 300)
Estimates Blood Loss in mL	(87)	(0 – 1000)
Intra-operative Complication	1	0
Nerve Spare		
Bilateral	318	61.1
Unilateral	175	33.7
Wide resection	27	5.2
Final Pathology**		
Gleason 3+3	110	21.2
Gleason 3+4	322	61.9
Gleason 4+3	57	10.9
Gleason >8	30	5.8

	Number / (median)	% / (range)
Pathology T Stage**		
≤T2	403	77.5
T3a	96	18.5
T3b	20	3.8
BCR	35	6.5

*One biopsy omitted: intraductal carcinoma ** One pathology omitted

Table 2: Erectile Dysfunction (ED) at 12 months against NeuroSAFE Bundles spared/removed:

	ED Score 0	ED Score 1	ED Score 2	ED Score 3	Total
NVB spared	41 (13.4%)	88 (28.9%)	94 (30.8%)	82 (26.9%)	305 (100%)
1NVB taken	10 (9.3%)	26 (24.1%)	31 (28.7%)	41 (38%)	108 (100%)
2NVBs taken	0 (0%)	1 (5.9%)	4 (23.5%)	12 (70.6%)	17 (100%)

p-value = <0.01

ED Score 0=spontaneous erections;1=erections with PDE-51;2=partialerection;3=no/minimal erections

Table 3: Urinary Continence at 12 months against NeuroSAFE Bundles spared/removed:

	Continence Score 0	Continence Score 1	Continence Score 1.5	Continence Score 2	Continence Score 3	Total
NVB spared	170 (55%)	100 (32.4%)	10 (3.2%)	18 (5.8%)	11 (3.6%)	309 (100%)
1NVB taken	65 (58.6%)	36 (32.4%)	3 (2.7%)	5 (4.5%)	2 (1.8%)	111 (100%)
2 NVBs taken	9 (50%)	8 (44.4%)	1 (5.6%)	0 (0%)	0 (0%)	18 (100%)

p-value = 0.49

Continence Score 0=pad free;1=safety;1.5=1pad/day;2=2-3pads/day;3=4or more pads/day

Table 4: Whole Gland PSM against NeuroSAFE NVB spared/removed:

	NO PSM	PSM	Total
NVBs spared	275 (79%)	73 (21%)	348 (100%)
1 NVB removed	107 (79.8%)	27 (20.1%)	134 (100%)
2 NVBs removed	15 (83.3%)	3 (16.7%)	18 (100%)

p-value = 0.98

Table 5: Concordance of Frozen Section with paraffin wax.

	Paraffin Positive	Paraffin Negative	
Frozen Section Positive	147	13	Positive Predictive Value = 91.8%
Frozen Section Negative	7	672	Negative Predictive Value = 98.9%

	Paraffin Positive	Paraffin Negative	
	Sensitivity = 95.5%	Specificity = 98.1%	

Table 6: Concordance of Positive Frozen Section length with paraffin wax result.

	Paraffin Positive	Paraffin Negative	
Median Frozen Section Positive margin (range)	6mm (0.5 -23)	2.5mm (0.1 – 12)	

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