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Robot-assisted prostate-specific membrane antigen-radioguided surgery in primary diagnosed prostate cancer

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ABSTRACT

Objectives

To evaluate the safety and feasibility of ^{99m}Tc-based prostate-specific membrane antigen (PSMA) robot-assisted radioguided surgery to aid or improve the intraoperative detection of lymph node metastases during primary robot-assisted radical prostatectomy (RARP) for prostate cancer (PCa).

Materials and Methods

Men with primary high-risk Pca (≥cT3a, international society of urological pathology (ISUP) Grade Group ≥3 or PSA of ≥ 15 ng/mL) with potential lymph node metastasis (Briganti nomogram risk >10% or on preoperative imaging) were enrolled onto the study. Patients underwent a staging ^{68}Ga-PSMA PET/CT. Pre-operatively a ^{99m}Tc-labelled PSMA ligand (^{99m}Tc PSMA I&S; 500 MBq) was administrated followed by single-photon emission/CT(SPECT). A RARP including extended pelvic lymph node dissection was performed, with intraoperative tracing of PSMA-avid tissues using a prototype DROP-IN gamma probe. Resected specimens were also measured ex-vivo. Histopathological concordance with probe findings was evaluated. A radiotracer count of ≥ 1.5 times the background reference (in-vivo), and ≥10 (absolute count) in the ex-vivo setting, was considered positive.

Results

Twelve patients were included, median age of 68 years and PSA of 9.15 ng/ml. The majority of patients harboured ISUP 5 PCa (75%) and had avid lymph nodes on pre-operative PSMA PET (64%). The DROP-IN probe aided resection of PSMA-avid (out-of-template) lymph nodes and residual disease at the prostate bed. 11 metastatic lymph nodes were identified by the probe that were not observed on pre-operative ^{68}Ga-PSMA PET/CT. Of the 74 extraprostatic tissue specimens that were resected, 22 (29.7%) contained PCa. The sensitivity, specificity, PPV and NPV (95% confidence interval) of inpatient use of the gamma probe was 76% (53-92%), 69% (55-81%), 50% and 88%, respectively. Ex-vivo, the diagnostic accuracy was superior, 76% (53-92%), 96% (87-99%), 89% and 91%, respectively. Of the missed lymph nodes in-vivo (n=5) and ex-vivo (n=5), 90% were micrometastasis (≤3mm). No complications occurred greater than Clavien-Dindo Grade I.

Conclusion

Robot-assisted 99mTc-based PSMA radioguided surgery is feasible and safe in the primary setting, optimizing the detection of nodal metastases at the time of RARP and ePLND. Further improvement of the detector technology may optimize the capabilities of robot-assisted ^{99m}Tc-based PSMA-radioguided surgery.

Key Words

Image-guided surgery, prostate-specific membrane antigen, prostate cancer, robot-assisted surgery, extended pelvic lymph node dissection

INTRODUCTION

The ability to accurately determine the location and extent of lymph node involvement in prostate cancer (PCa) has significant implications on decision-making regarding treatment modality and planning. In men with higher risk PCa, bilateral extended pelvic lymph node dissection (ePLND) during robot-assisted radical prostatectomy (RARP) remains an important staging procedure (*1*). Additionally, ePLND has been observed to provide a chance of cure in patients with limited nodal metastases (*2,3*). Despite these valuable considerations, ePLND has several shortcomings. Importantly, ePLND is associated with increased patient morbidity (*4*). The extent of dissection has an impact on the detection and removal of any nodal disease (*5*). Even with an extended template dissection, 35% of lymph nodes (potentially containing PCa) will not be removed at the time of surgery, either being out of the surgical template or being missed within it (*6*).

The emergence of prostate-specific membrane antigen positron emission tomography computed tomography (PSMA PET) has greatly improved the detection of small lymph node metastases when compared to conventional imaging. Whilst PSMA PET imaging has demonstrated excellence for the detection of lymph node metastases in the setting of both primary staging and biochemical recurrence (BCR), it is intrinsically limited by its spatial resolution of 2-4 mm given radioisotope decay and detector distance from the tumour (*7,8*). Several studies correlating pre-operative PSMA PET findings to histopathological findings from a subsequent ePLND have demonstrated poor sensitivity in the detection of <4 mm nodal metastases (*9-11*). Other studies showed that patients with nodal metastatic disease on PSMA PET/CT have an increased risk of developing BCR after RARP (*12*). It may be in the subset of patients with limited nodal micro-metastases (1-2 nodes) that are most likely to benefit from an (optimized) ePLND (*3*).

PSMA-targeted radioguided surgery has been suggested as an auxiliary technique to improve the intraoperative detection and clearance of lymph nodes harbouring (limited) metastatic disease. Recently, Maurer et al. described the use of technetium-99m (^{99m}Tc) based PSMA-radioguided surgery in the setting of an open salvage ePLND following BCR after surgery with promising results, detecting metastatic deposits as small as 3 mm (*13*). Using a new DROP-IN gamma detector technology, it has been possible to translate radioguided surgery to

the robotic setting (*14,15*). This raised the question as to whether ^{99m}Tc based PSMA-radioguided surgery in the primary treatment setting could improve treatment outcomes by optimizing metastatic lymph node detection and clearance. Furthermore, no data exists on the ability to perioperatively detect significant positive surgical margins.

To date there are no results of prospective trials evaluating the radioguided identification of lymph node metastases at the time of RARP and ePLND in the primary treatment setting. The DETECT trial is a single site, prospective pilot study that aimed to describe the technique and feasibility of robot-assisted radioguided surgery using the molecular targeting of PSMA to aid intraoperative localisation of nodal metastases at the time of RARP and ePLND in a primary treatment setting.

MATERIALS AND METHODS

Study Population

Twelve men with histologically proven PCa and potential lymph node metastasis were included in this prospective clinical trial between July 2019 and May 2021. Men ≥18 years old with high risk PCa (≥cT3a or International Society of Urological Pathology (ISUP) Grade Group ≥3 or preoperative PSA ≥ 15 ng/mL), with a Briganti nomogram risk of ≥ 10% were included in the trial. Exclusion criteria were prior PCa treatment, evidence of distant (lymph node) metastatic disease. Institutional review board approved this study (HREC/16/SVH/157) and written informed consent was obtained from all men. The trial is registered at ANZCTR (ACTRN12621001728820) and funding was obtained from the Prostate Cancer Foundation of Australia.

Pre-operative Radiotracer Administration and Imaging

Patients underwent a ^{68}Ga-PSMA PET/CT scan as part of preoperative staging (<3 months before surgery). These scans were centrally reviewed by 2 experienced nuclear physicians that were blinded for pathology. In case of conflicting results, a second consensus read was performed. Patients underwent an intravenous administration of 500 MBq ^{99m}Tc-labelled PSMA targeted ligand (^{99m}Tc PSMA I&S) approximately 18 hours before surgery (*16*). On the morning of their surgery, single-photon emission computerised tomography scan (SPECT)/CT imaging was

performed to cross-validate the findings of the pre-operative ^{68}Ga-PSMA PET/CT scan and to serve as a quality control for radiotracer injection and distribution. The results of the ^{99m}Tc-PSMA SPECT/CT were not used to guide surgery. In patients suspected of harbouring metastatic disease in out-of-template mesorectal lymph node regions, a percutaneous CT-guided hookwire was inserted at time of ^{99m}Tc-PSMA SPECT/CT to assist localisation at time of dissection.

Surgical Procedure

Patients underwent a RARP and ePLND via a standard six-port, transperitoneal approach with a four-arm da Vinci XI system (Intuitive Surgical Inc., USA). A prototype DROP-IN gamma probe connected to the Europrobe 3.2 console (Eurorad, S.A.)(Figure 1a.) was inserted through a 12 mm assistant port via the Alexis laparoscopic system (Applied Medical Corp., USA) placed above the left iliac crest (Figure 1b.) (*15,17*). Once inserted, the drop-in gamma probe (Figure 1c & d.) was articulated with the use of da Vinci ProGrasp forceps to take measurements. Real-time feedback was provided both acoustically and numerically via a read-out console placed in the surgical theatre. Before resection, gamma probe measurements were systemically taken at the anterior abdominal wall muscle as a background reference measurement, at each template lymph node site (external iliac, internal iliac and obturator pelvic lymph nodes) bilaterally, the prostate, the prostate bed following resection and other out-of-template sites clinically suspected of harbouring disease (based on preoperative imaging). To exclude the influence of in-vivo background interference, ex-vivo gamma probe measurements were taken of each resected tissue specimen using the same DROP-IN probe.

Histopathological Correlation with ^{99m}Tc-PSMA Gamma Probe Measurements

Histopathological evaluation was performed by a specialist uro-pathologist blinded to preoperative imaging and gamma probe findings. Regions with gamma probe measurements were correlated with final tissue histopathological findings on a per region basis. Several radiotracer cut-offs were evaluated on their diagnostic performance as no literature existed on the radiotracer activity count in the primary treatment setting. Probe findings were rated positive when tissue specimens had a radiotracer activity count of ≥ 1.5 times the background reference value in the in-vivo setting and ≥ 10 (absolute count) in the ex-vivo setting.

Follow-up

Patients were first followed-up at 6 weeks post-operatively. Subsequent interval PSA measurements and/or adjuvant therapy was determined by their treating urologist based on their biochemical response and final pathology. A BCR following surgery was defined as PSA >0.1 ng/mL after initial biochemical control. In case of persistent PSA following surgery (PSA >0.1 ng/mL) or BCR, adjuvant pelvic radiotherapy with ADT was discussed. Post-operative complications were categorised by Clavien-Dindo classification. Any subsequent PSA measurements or adjuvant therapy was monitored during the course of this study.

Statistical Analyses

Preoperative imaging and DROP-in gamma probe results were compared to corresponding final pathology. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were derived from 2x2 contingency tables. Quantitative data are reported as the median value and interquartile ranges. Categorical data are reported as absolute and relative frequencies. Differences in radiotracer counts between malignant and benign tissue was compared with a Chi-Square test. All statistical analyses were conducted with the SPSS Statistical Software Package (Version 26.0. IBM).

RESULTS

Pre-operative Patient Characteristics

Pre-operative patient characteristics are summarised in Table 1. The median age was 68 (interquartile range 57 – 69) years and pre-operative PSA was 9.15 (6.0 – 21.2) ng/ml. Nine patients had ISUP 5 and three patients had ISUP 4 PCa. Seven patients demonstrated evidence of pelvic nodal disease on ^{68}Ga-PSMA PET/CT across 11 anatomical regions. Four of those lesions were within the standard ePLND template whilst the other 7 lesions were outside the standard surgical template (mesorectal, presacral, below the aortic bifurcation). In Figure 2. an example of a mesorectal node was shown. Due to the known limitations (sensitivity and resolution) of ^{99m}Tc-

PSMA SPECT/CT, only 4 lesions were observed on ^{99m}Tc-PSMA SPECT/CT (*18*). These corresponded with large lymph nodes (>9 mm) on ^{68}Ga-PSMA PET/CT and were all histologically confirmed as cancer.

Safety Outcomes

No post-operative complications > Clavien-Dindo Grade 1 were observed in the follow-up period. Only 1 patient suffered from a surgical post-operative complication (lymphoedema) that was conservatively managed. No complications relating to the administration of ^{99m}Tc-PSMA radiotracer or the use of the prototype DROP-IN gamma probe were seen.

^{99m}Tc-PSMA Gamma Probe Guidance during Surgery and Concordance with Pre-operative Imaging

A total of 11 pre-operative lesions were visible on ^{68}Ga-PSMA PET/CT and 8 demonstrated metastatic disease on final histopathology. Of the remaining 3 lesions, 2 lesions (both in patient 11) demonstrated no disease (however the patient had persistent PSA following surgery, therefore the lesions may not have been surgically removed) and the other lesion (Patient #10, left mesorectal node) was irresectable. In contrast, 11 metastatic lymph nodes were identified by in-vivo and ex-vivo use of the probe that were not observed on pre-operative ^{68}Ga-PSMA PET/CT, with one lymph node harbouring 15mm of PCa.

The DROP-IN gamma probe was utilised in-vivo in patient #2 to correctly identify 6mm residual PCa at the right apical margin of the prostate bed that would have otherwise remained undiscovered (Figure 1d.). For 2 patients the probe was successfully used in conjunction with percutaneously placed hookwires to localise metastatic out-of-template mesorectal lymph nodes.

^{99m}Tc-PSMA Gamma Probe Concordance with Extended Pelvic Lymph Node Histopathology

Detailed gamma probe findings with histopathological correlation in the in-vivo and ex-vivo setting are included in supplementary tables 1 and 2, respectively. A total of 74 extraprostatic (nodal packages and periprostatic tissue) specimens were resected (median 6 per patient, 5 – 7) which included 213 lymph nodes (median 17 per patient, interquartile range 12 – 22).

Twenty-two of the 74 resected specimens (29.7%) demonstrated evidence of PCa on histopathology. Histopathology positive specimens had a median in-vivo and ex-vivo count of 35 (20 – 63) and 19 (8 – 29), while negative specimens showed a median in-vivo and ex-vivo count of 17 (10 – 34) and 4 (1 – 6) respectively. This was not statistically significantly different in-vivo (p=0.32) whilst being significantly different ex-vivo (p=0.001). The signal-to-background ratio was 2.1 during surgery (in-vivo) and 4.8 ex-vivo.

In-vivo the DROP-IN probe readings were rated positive in 32 locations. Of these positive locations, 16 contained Pca whilst 16 contained no cancer. The DROP-IN probe readings were rated negative in 41 locations, of which 36 contained no cancer and 5 harboured Pca. This resulted in an in-vivo sensitivity, specificity, PPV and NPV of 76% (95% confidence interval (CI): 53% - 92%), 69% (95% CI: 55% to 81%), 50% and 88%, respectively. The locations of false positive results varied between patients (Supplementary table 1).

Ex-vivo, with no background signal from the body, a superior accuracy was observed using the same probe. DROP-IN probe readings were rated positive in 18 resected specimens. Of these positive specimens, 16 contained PCa whilst only 2 contained no PCa. The DROP-IN probe readings were rated negative in 55 specimens, of which 50 contained no PCa and 5 harboured PCa. This resulted in an ex-vivo sensitivity, specificity, PPV and NPV of 76% (95% CI: 53% - 92%), 96% (95% CI: 87% - 99%), 89% and 91%, respectively.

The median size of metastatic foci that were correctly identified by probe was 9mm (interquartile range 6.5 – 11.2) for both in-vivo and ex-vivo use. The smallest nodes detected in-vivo and ex-vivo were 0.4mm and 0.1mm, respectively. In the 5 specimens with metastatic disease that the probe did not detect in-vivo, none were avid on either ^{68}Ga-PSMA PET/CT or ^{99m}Tc-PSMA SPECT/CT and this indicates low tracer uptake. While the tracer uptake in 4 of these instances could be related to size (Patients #1, #2 and #8: <1mm, Patient #2: 3mm), the other 6mm metastatic lesion could be due to low PSMA expression (Patient #8). In the 5 specimens with metastatic disease that were unsuccessfully detected by the probe ex-vivo, none were avid on either ^{68}Ga-PSMA PET/CT or ^{99m}Tc-PSMA SPECT/CT, probably due to size (<3mm).

Follow-up and Oncological Outcomes

Median follow-up was 13 months (4 – 22) after surgery. At 6 weeks post-surgery, five of the 12 patients had an undetectable PSA (<0.03 ng/mL), 2 patients had an equivocal PSA persistence (<0.1, ≥0.03 ng/mL) and 5 patients had a persistent PSA (>0.1 ng/mL). All 5 patients that had a complete metabolic response had no BCR during follow-up and required no adjuvant therapy. Final pathology in those 5 patients showed limited lymph node metastasis in 80% (patient# 1,6,8,9,12, supplementary table 1&2).

The two patients with equivocal PSA persistence following surgery experienced both a BCR. Of the 7 patients with detectable PSA (BCR n=2, persistent PSA n=5), six patients received ADT in combination with adjuvant radiotherapy as part of multimodal therapy whilst the remaining patient was ineligible to receive adjuvant radiotherapy. Of these 7 patients, three have a complete metabolic response (after withdrawal from hormonal treatment >12 months) and the remaining four patients are still on ADT as part of their adjuvant therapy and therefore cannot be biochemically assessed. At present none of the included patients have metastatic disease, PCa-specific and overall mortality is 0%.

DISCUSSION

To our knowledge this is the first prospective series on robot-assisted PSMA-targeted surgery and ePLND in the primary treatment setting. Prior PSMA-targeted surgery studies were performed in the salvage pelvic lymph node and local recurrence dissection setting (*13,19,20*). The technical setup used in our study is a combination of Meershoek et al. (robotic use of DROP-IN gamma probe) and Maurer et al. (PSMA-radioguided surgery during open surgery) (*13,17*). A small gamma probe head is “dropped in” to the abdominopelvic cavity through an Alexis working port and manipulated using the da Vinci ProGrasp forceps. Using this technique, we were able to identify the far majority of the PSMA-PET avid foci (> 3mm), indicating that the DROP-IN technology can bridge pre-and intraoperative findings. Interestingly, the probe helped identify 11 foci that were not seen on PSMA PET/CT or SPECT. Nevertheless, not all foci could be identified but particularly micrometastasis (foci <3mm) were missed.

The propensity for PSMA-targeted approach to miss small PSMA-PET negative foci suggests this approach cannot substitute final histopathological analysis. Consequently, PSMA-radioguided surgery may not safely omit

probe negative template regions from standard ePLND. From our results to date, we still advise that the complete ePLND template should be surgically removed and be indicated by preoperative nomograms (e.g. Briganti). However, the aim of the DROP-IN probe development was to aid resection of preoperative identified lesions on PSMA PET CT, and potentially improve the sensitivity to detect pelvic lymph node metastasis during surgery.

A significantly poorer specificity of the probe was observed in-vivo when compared to the very high specificity seen ex-vivo. Only 1 false positive probe measurement was observed ex-vivo. Consistent with prior literature findings, this is most likely due to the pharmacokinetics of ^{99m}Tc-PSMA-I&T, which results in in-vivo background radiotracer activity (*1*). Probe measurements were extremely sensitive to any angulation towards secondary sources of radiotracer activity. Particularly the prostate (basal PSMA-expression; median count 95), bladder and ureters (^{99m}Tc-PSMA-I&S is renally excreted). Prostate background could be neutralized by first performing a RARP, but this then comes with urine contaminations. Altogether this suggests that in-vivo performance can be improved, by either refining the detector or using a tracer with less background uptake.

Compared to radioguided sentinel node identification studies, including those using the same prototype DROP-IN gamma probe, this study indicates that not only the effect of background signals is more explicit for PSMA-directed resections, but also the absolute count rates are up to ten-fold lower (*15*). The combination of these features complicated identification of foci. From Supplementary tables 1 and 2 it can be concluded that no single radiotracer cut-off would include all true positive and negative results. The radiotracer activity count cut-off at SBR > 1.5 as applied in this study was aimed to identify most regions containing lymph node metastasis. As the tracer pharmacokinetics are defined, and may be subject to individual variation, further refinement of the detector technology could help resolve these issues. Another consideration is the use of alternative PSMA-targeting tracers that do not suffer from deeper lying background signals (*21*). In a recent series potential mitigation of such interference was explored (ex-vivo) by employing ^{68}Ga-PSMA-11 as a radiotracer, with a novel drop-in beta probe utilising the limited tissue penetration exhibited by beta particle emission (*22*). Their findings demonstrated high beta radiation attenuation when >1.5 mm of normal tissue separated probe from tumour. Further work is required to evaluate if this remains feasible in aiding the in-vivo detection of PCa. Future development of fluorine-18-based PSMA targeting radiotracer detectable by such a beta probe could serve to abate background urinary activity (*22*).

A down side of this approach is that the surgical staff is exposed to 511keV radiation doses. As fluorescence is also attenuated by tissue, tracers that contain a ^{99m}Tc and fluorescent signature may help improve the accuracy in the future (*23*).

With consideration of the high ex-vivo specificity, we conclude that one of the most promising uses of this technology is ex-vivo probe confirmation of removal of suspicious metastatic nodes identified on pre-operative ^{68}Ga-PSMA PET at the time of ePLND. Negative ex-vivo probe measurements should prompt further in-vivo assessment and consideration of regional re-resection. Furthermore, the in-vivo utility of the probe in detecting out-of-template lymph nodes in surgically challenging regions was valuable. In 2 patients, the probe was crucial in the detection of deep mesorectal lymph nodes avid on pre-operative ^{68}Ga-PSMA PET/CT and deemed unlikely to be achievable by the pre-inserted hookwire alone. With the emergence of PSMA PET/CT imaging, PCa metastases to mesorectal lymph nodes have been demonstrated to be more prevalent than previously thought and may occasionally be included in lymph node dissections (*24*).

Lastly, we found that examination of the prostate bed following prostatectomy was a useful manoeuvre to evaluate surgical margins. A small focus of tissue at the right apical prostate demonstrated high counts upon inspection with the drop-in probe and found to harbour residual cancerous tissue in patient #2. Caution need to be taken given potential urinary contamination of the ^{99m}Tc-PSMA radiotracer.

The limitations of our study include limited cohort size and short-term follow-up. This especially impacts the oncological results. Additionally, given the novelty of this study, many technical aspects remain relatively experimental, including the time interval from radiotracer administration to surgery, positive threshold count values and learning curve associated with intraoperative probe manipulation. Despite these limitations, the use of this technique has been observed to be safe and feasible throughout the study period with promising short-term oncological results. Whether an improved oncological resection by PSMA-guided radiosurgery results in superior long-term oncological outcomes, especially in the era of PSMA PET-directed whole pelvis radiotherapy, can only be derived from a prospective randomized trial. This also comprises the query that potential (mesorectal) dose reduction in adjuvant radiotherapy results in less patient morbidity.

Based on the preliminary results we have decided to redesign the study towards patients suspected of lymph node metastasis on preoperative imaging and/or those with locally advanced disease in which the probe may detect residual PCa after removal of the prostate. Further technological advancement of the drop-in probe and radiotracers convinced us to prematurely close this study and evaluate these developments in the aforementioned patient population.

CONCLUSION

^{99m}Tc-based PSMA radioguided surgery is both feasible and safe in aiding the detection of nodal metastases at the time of primary robot-assisted RP and ePLND for higher risk PCa. Preliminary experience of this technology in the primary setting has found it valuable for intra-operative detection of suspected (out-of-template) lymph nodes and particularly in ex-vivo confirmation of successful resection of malignant nodes. Furthermore, it was also able to detect residual cancerous tissue in the prostate bed following prostatectomy. PSMA-radioguided surgery holds promise for improving the intraoperative identification and removal of PCa tissue.

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Financial Disclosure

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Conflict of Interest

None of the authors have a conflict of interest to declare.

KEY POINTS

Question: Is it safe and feasible to aid or improve the intraoperative detection of lymph node metastases during primary robot-assisted radical prostatectomy with ^{99m}Tc-based PSMA robot-assisted radioguided surgery?

Pertinent Findings:

^{99m}Tc-based PSMA robot-assisted radioguided surgery was safe and aided resection of PSMA-avid (out-of-template) lymph nodes and residual disease at the prostate bed.

Additional metastatic lymph nodes were identified by the probe that were not observed on pre-operative ^{68}Ga-PSMA PET/CT, whilst predominantly micrometastasis were missed.

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Figure 1.

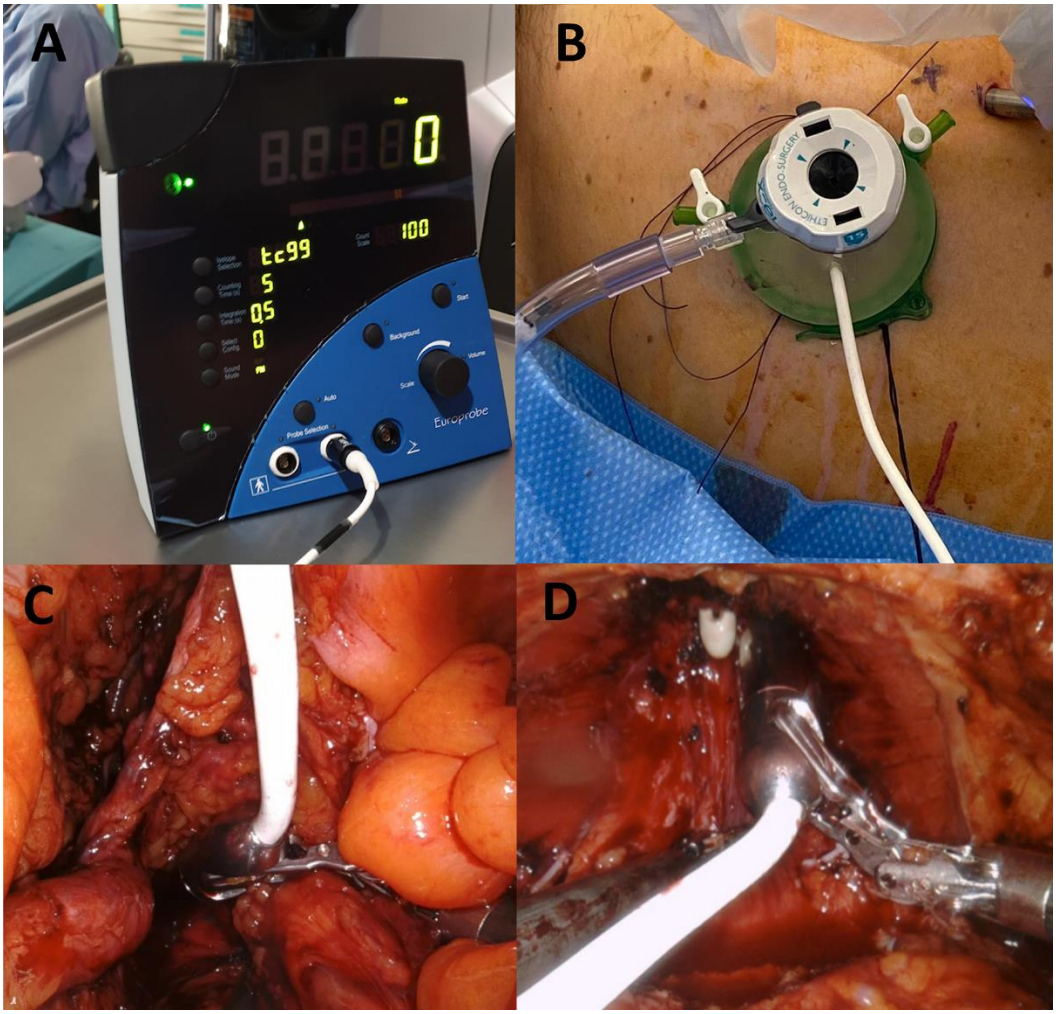

Figure 1a. Europrobe 3.2 console (Eurorad, S.A.) providing visual and acoustic count feedback. b. Insertion of drop-in gamma probe and 12 mm assistant laparoscopic port through the Alexis system. c &d. Intraoperative use of the drop-in gamma probe to obtain counts from the left obturator lymph node template region and the prostate bed, respectively.

Figure 2.

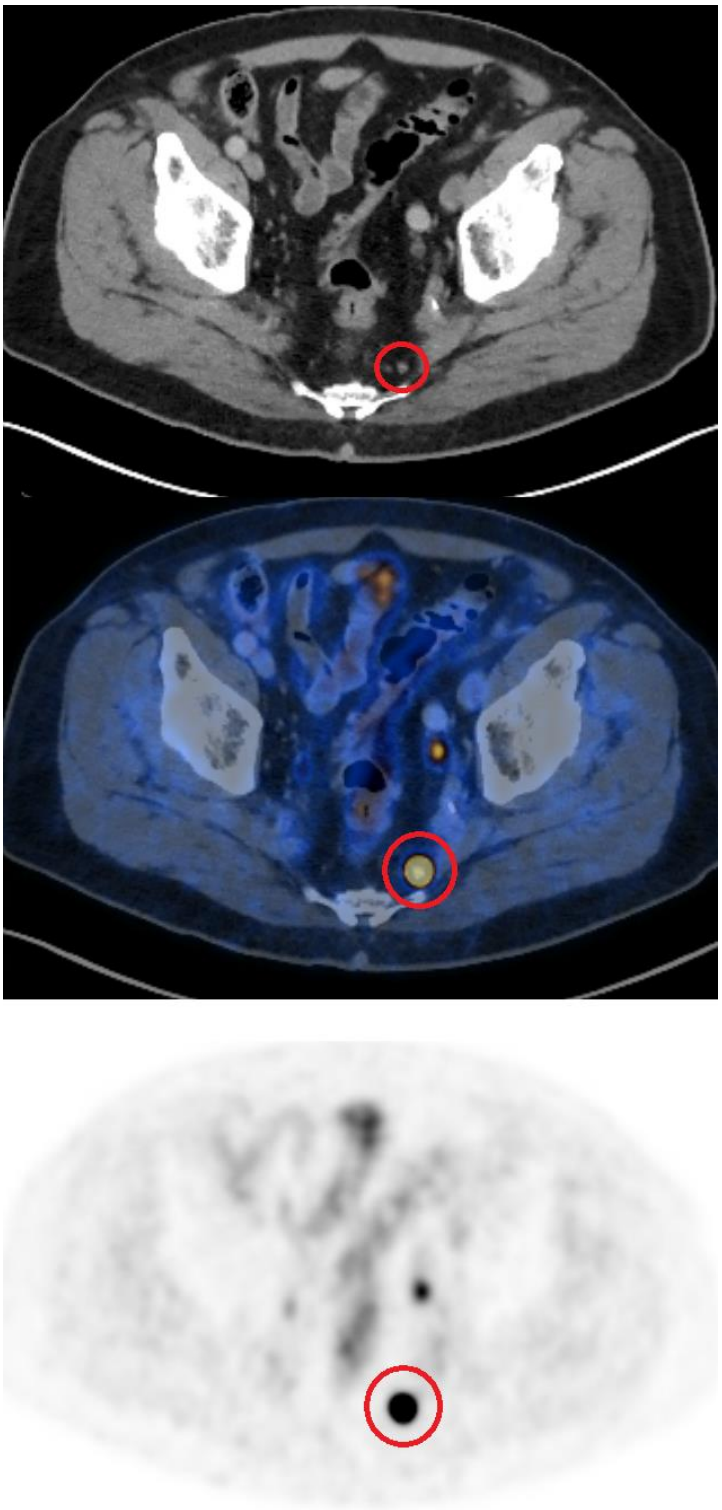

Figure 2. Suspicion for left mesorectal lymph node involvement on pre-operative ^{68}Ga-PSMA PET/CT in patient #12 (SUVmax 49). The probe successfully identified the node (in-vivo node count of 183) and final pathology showed a 8mm malignant lymph node.

Patient #	Age	PSA (ng/mL)	Gleason score	Clinical stage	^{68}Ga-PSMA PET/CT avid lymph node region (SUV_{max})	^{99m}Tc-PSMA SPECT/CT avid regions
1	68	7.3	4+5=9	T2bN0M0	Nil	Nil
2	64	58	4+5=9	T2bN0M0	Nil	Nil
3	73	15	4+5=9	T2bN1M0	Nil	Nil
4	55	10	4+4=8	T2bN1M0	R external iliac (3.7)	Nil
5	68	8.3	5+4=9	T3bN1M0	L mesorectal (5.1)	L mesorectal
6	56	11	4+5=9	T1cN0M0	Nil	Nil
7	63	6.7	4+4=8	T2aN1M0	R mesorectal node (4.4)	Nil
8	69	46	4+5=9	T3bN1M0	Nil	Nil
9	69	3.9	4+5=9	T3bN1M0	R obturator (6.4)	R obturator
10	69	6	4+4=8	T1cN1M0	L mesorectal (3.8)	Nil
11	55	23.3	4+5=9	T3aN1M0	L obturator (3.4) Presacral (8.3, 3.4, 3.5) L mesorectal (3.3, 4.0) R internal iliac (4.0, 10) Oartic bifurcation (53)	Presacral Oartic bifurcation
12	71	5.1	4+5=9	T2aN1M0	L Presacral (49)	Nil

Table 1. Preoperative patient characteristics.

In-vivo use of gamma probe						
Patient #	**Background reference count**	**Template positive nodal regions (count)**	**Template negative nodal regions (count)**	**Other regions (count)**	**Metastatic cancer deposit locations (nodes)**	**Size of cancer**
1	10	Nil	LEI (8) LII (6) LO (6) REI (9) RII (9) RO (9)	Nil	LEI (1)	0.7 mm
2	10	Nil	LEI (8) LII (5) LO (6) REI (9) RII (3) RO (6)	Right paraurethral prostate bed (20)	REI (2) RO (2) R paraurethral prostate bed (1)	3 mm 0.6 mm 6 mm
3	7	LEI (17) REI (35) RII (20) RO (32)	LII (10) LO (7)	Nil	RII (1) RO (1)	3 mm 9 mm
4	10	LEI (25) LII (19) LO (15) REI (40) RII (25)	RO (7)	Nil	LEI (1) REI (1)	0.4 mm 15 mm
5	20	LEI (30) LO (35) RII (30)	LII (20) REI (25) RO (29)	Left mesorectal node (100)	LEI (1) LO (3) L mesorectal node (1)	12 mm 15 mm 9 mm
6	10	LO (18) REI (16)	LEI (10) LII (18) RII (10) RO (13)	Nil	Nil	Nil
7	10	RII (40) RO (50)	LEI (10) LII (10) LO (10) REI (6)	R mesorectal (49)	R mesorectal node (2)	6 mm
8	70	REI (150)	LEI (70) LII (70) LO (70)	Nil	LO (1) REI (1) RII (1)	6 mm 9 mm 0.1 mm

			RII (60) RO (60)			
9	8	LEI (18) LII (18) LO (45) REI (20) RII (17) RO (65)	Nil	Nil	RO (2)	9 mm
10	14	Nil	LEI (15) LII (14) LO (16) REI (14) RII (14) RO (17)	Nil	Nil	Nil
11	10	LEI (32) LII (32) LO (20) RII (38) RO (20)	REI (8)	Left mesorectal (22) Left sacral (29) Aortic bifurcation not measured Right paravesical (40)	LO (1) RII (1) RO (1) Aortic bifurcation (2) Paravesical (1)	9 mm 9 mm 12 mm 12 & 0.5 mm 8 mm
12	61	Nil	LEI (76) LII (71) LO (78) REI (64) RII (70) RO (68)	Left presacral (183)	Presacral (1)	8 mm

Supplementary table 1. Probe evaluation compared to histopathology in-vivo. A count of ≥ 1.5 times the background reference count was considered a positive probe finding. Abbreviations: LEI – left external iliac lymph nodes, LII – left internal iliac lymph nodes, LO – left obturator lymph nodes, REI – right eternal iliac lymph nodes, RII – right internal iliac lymph nodes, RO – right obturator lymph nodes.

Ex-vivo use of gamma probe					
Patient #	**Template Positive nodal regions (count)**	**Template Negative nodal regions (count)**	**Other regions (count)**	**Metastatic cancer deposit locations (no. of nodes)**	**Size of cancer**
1	Nil	LEI (3) LII (1) LO (1) REI (0) RII (2) RO (3)	Nil	LEI (1)	0.7 mm
2	Nil	LEI (1) LII (1) LO (2) REI (0) RII (1) RO (1)	Right paraurethral prostate bed (10)	REI (2) RO (2) Right paraurethral prostate bed (1)	3 mm 0.6 mm 6 mm
3	RO (14)	LEI (2) LII (1) LO (1) REI (0) RII (0)	Nil	RII (1) RO (1)	3 mm 9 mm
4	REI (28)	LEI (5) LII (5) LO (5) RII (7) RO (0)	Nil	LEI (1) REI (1)	0.4 mm 15 mm
5	LEI (10) LO (11)	LII (0) REI (0) RII (4) RO (4)	Left mesorectal node (70)	LO (3) LEI (1) L Mesorectal node (1)	12 mm 15 mm 9 mm
6	Nil	LEI (0) LII (10) LO (6) REI (5) RII (5) RO (4)		Nil	Nil
7	Nil	LEI (0) LII (4) LO (4)	R mesorectal (26)	R mesorectal node (2)	6 mm

		REI (0) RII (6) RO (6)			
8	LO (30) REI (30) RII (21)	LEI (0) LII (7) RO (4)	Nil	LO (1) REI (1) RII (1)	6 mm 9 mm 0.1 mm
9	RO (35)	LEI (0) LII (9) LO (9) RII (0) REI not resected	Nil	RO (2)	9 mm
10	Nil	LII (4) LO (0) RII (6) RO (4) LEI & REI not resected	Nil	Nil	Nil
11	LII (200) LO (20) RII (14) RO (19)	LEI (3) REI not resected	Left mesorectal (3) Left sacral (5) Right paravesical (20) Aortic bifurcation not measured	LO (1) RII (1) RO (1) Aortic bifurcation (2) Paravesical (1)	9 mm 9 mm 12 mm 12 & 0.5 mm 8 mm
12	Nil	LEI (8) LII (8) LO (8) REI (7) RII (7) RO (7)	Left presacral (381)	Presacral (1)	8 mm

Supplementary table 2. Probe evaluation compared to histopathology ex-vivo. An absolute count of ≥ 10 was considered a positive probe finding. Abbreviations: LEI – left external iliac lymph nodes, LII – left internal iliac lymph nodes, LO – left obturator lymph nodes, REI – right eternal iliac lymph nodes, RII – right internal iliac lymph nodes, RO – right obturator lymph nodes.

GRAPHICAL ABSTRACT