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# Initial multicentre experience of $^{68}$gallium-PSMA PET/CT guided robot-assisted salvage lymphadenectomy: acceptable safety profile but oncological benefit appears limited

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## Objectives

To evaluate the safety and short-term oncological outcomes of $^{68}$gallium-labelled prostate-specific membrane antigen ($^{68}$Ga-PSMA) positron-emission tomography (PET)/computed tomography (CT)-directed robot-assisted salvage node dissection (RASND) for prostate cancer oligometastatic nodal recurrence.

## Materials and Methods

Between February 2014 and April 2016, 35 patients across two centres underwent RASND for $^{68}$Ga-PSMA PET/CT-detected oligometastatic nodal recurrence. RASND was performed using targeted pelvic dissection, unilateral extended pelvic template or bilateral extended pelvic template dissection, depending on previous pelvic treatment and extent/location of nodal disease. Complications were reported using the Clavien–Dindo classification system. Definitions of prostate-specific antigen (PSA) treatment response to RASND were defined as 6-week PSA <0.2 ng/mL (broad definition) or PSA <0.05 ng/mL (strict definition) in those who had undergone primary prostatectomy, and 6-week PSA level < post-radiotherapy nadir in those who had undergone primary radiotherapy. Biochemical recurrence (BCR) after RASND was defined as a PSA >0.2 ng/mL or PSA > nadir, for those who had undergone primary prostatectomy and primary radiotherapy, respectively. Predictors of treatment response were analysed using univariate binary logistic regression.

## Results

A total of 58 lesions suspicious for lymph node metastases (LNM) in 35 patients were detected on $^{68}$Ga-PSMA imaging. A total of 32 patients (91%) had histopathologically proven LNM at RASND, with a total of 87 LNM and a median (interquartile range) of 2 (1–3) LNM per patient. In all, eight patients (23%) experienced complications, all Clavien–Dindo grade ≤2. Treatment response was seen in 15 (43%) and 11 patients (31%), using the broad and strict definitions, respectively. BCR-free survival and clinical recurrence-free survival at a median follow-up of 12 months were 23% and 66%, respectively, for the entire cohort. Bilateral template dissection was the only significant univariate predictor of treatment response in our cohort.

## Conclusions

Although RASND appears safe and feasible, less than half of our cohort had a treatment response, and less than a quarter experienced BCR-free survival at 12-month median follow-up. $^{68}$Ga-PSMA imaging underestimates micro-metastatic disease, therefore RASND will rarely be curative. Strict patient selection and restricting RASND to clinical trials is recommended. Long-term follow-up from such trials is required to further assess potential quality of life and mortality benefits.

## Keywords

prostate cancer, biochemical recurrence, salvage lymph node dissection, $^{68}$Gallium-PSMA PET/CT scan, PSA response

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## Introduction

A significant proportion of patients undergoing curative treatment for prostate cancer (PCa) will develop biochemical recurrence (BCR) [1–3]. Novel positron-emission tomography (PET)/computed tomography (CT) techniques, in particular, $^{68}$gallium-labelled prostate-specific membrane antigen ($^{68}$Ga-PSMA) PET/CT, have improved staging compared with lower-sensitivity conventional imaging with plain CT and $^{99m}$technetium bone scan. This has enabled earlier detection of lymph node metastases (LNM) at lower volumes and lower PSA levels
[4–8]. It remains unknown whether LNM-targeted therapy for PCa recurrence can achieve prolonged BCR-free and clinical recurrence-free survival, improved quality of life (QoL) by delaying systemic therapy, and potentially even cure in a minority of patients. There is evidence from other cancers (e.g. colorectal cancer, sarcoma and RCC) that treatment of oligometastases may improve cancer-specific and overall survival [9].

Long-term survival in patients with metastatic PCa is greater in those with low-volume LNM than in those with more extensive nodal, bone or visceral metastases [10–13]. In oligometastatic node-only disease, this has led to investigation of metastases-directed therapy with either stereotactic radiotherapy or surgery, with a perceived favourable tumour phenotype in this low-volume metastases patient subgroup [9,14]. Although studies have been limited to mostly retrospective ones with no standard-therapy comparative group, a number of authors have described short-term oncological results from choline PET/CT-guided open pelvic and retroperitoneal salvage lymph node dissection (SLND) surgery, with varying outcome measures including PSA response, BCR-free survival, clinical recurrence-free survival and avoidance of systemic therapy [9,15]. Long-term survival data, however, are scarce at present.

Robot-assisted salvage node dissection (RASND) based on newer $^{68}$Ga-PSMA PET/CT imaging is a novel potential therapeutic option for selected patients with PCa oligometastatic nodal relapse. The aim of the present study was to evaluate the safety and short-term oncological efficacy of $^{68}$Ga-PSMA-directed RASND in patients who had previously undergone primary radical prostatectomy (RP) or radiotherapy.

## Patients and Methods

### Study Population

This multicentre retrospective study received institutional review board approval from the centres involved (St Vincent's Hospital, Sydney and the Wesley Hospital, Brisbane). Between February 2014 and April 2016, all patients who underwent RASND at each institution for $^{68}$Ga-PSMA PET/CT-detected oligometastatic node-only disease (1–5 lesions) were reviewed. All the patients had been previously treated for localized PCa with curative intent by either RP or radiotherapy. A number of patients had previously received short-course adjuvant or salvage androgen deprivation therapy (ADT) within 24 months of primary treatment. No patients were on ADT at the time of RASND, and similarly none were castrate-resistant.

### Detection of Disease Relapse after Primary Treatment

Clinical recurrence of PCa was detected by $^{68}$Ga-PSMA PET/CT, which was performed and analysed as per previously reported institutional protocols [4,5]. All the patients who had undergone primary radiotherapy had local PCa recurrence excluded by imaging and prostate biopsy. Figure 1 is an example of key images from a $^{68}$Ga-PSMA PET/CT in a patient with oligometastatic nodal disease in the present study cohort.

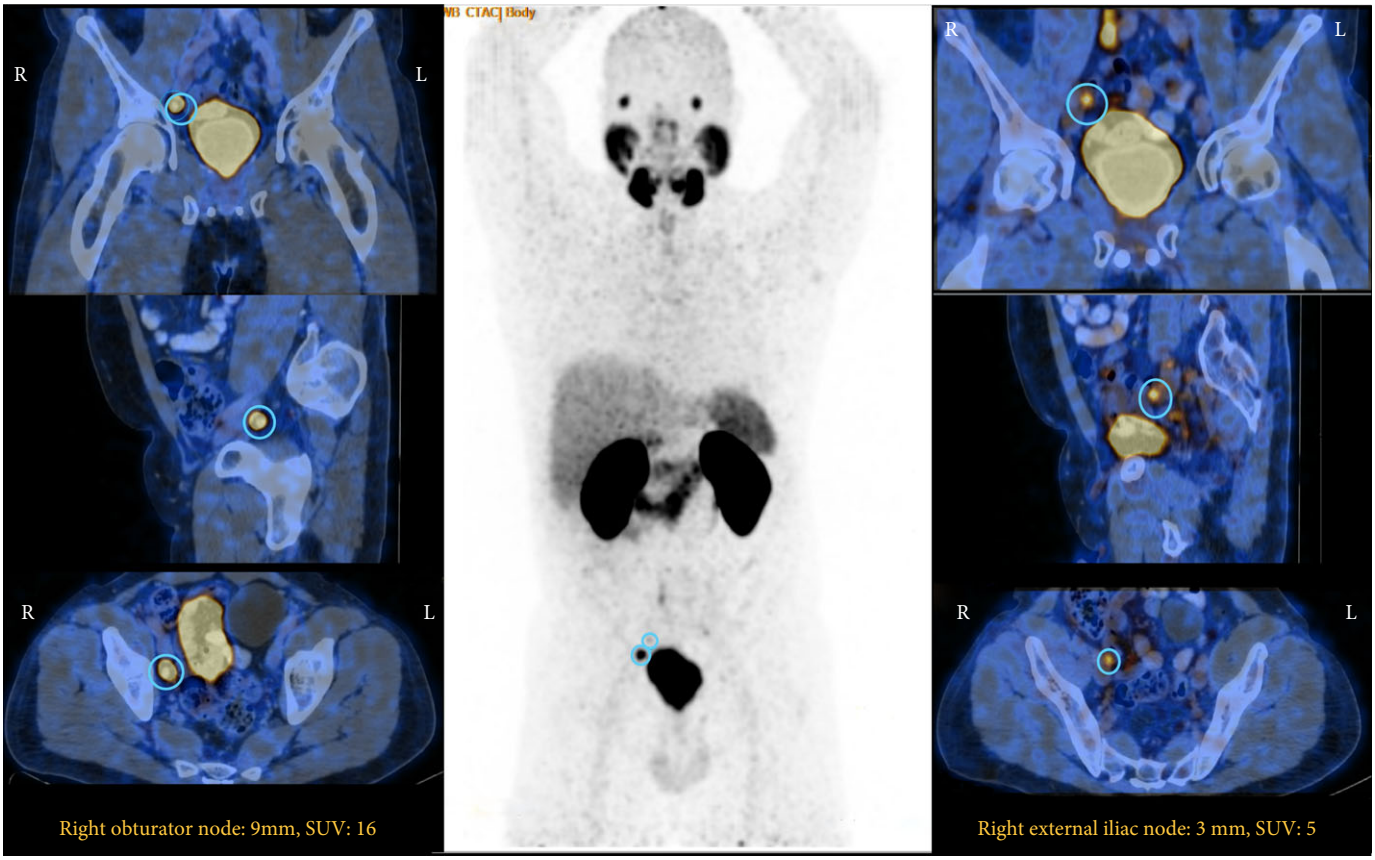
### Surgical Procedures and Histologic Evaluation

The da Vinci Surgical system was used with a six-port configuration to perform transperitoneal RASND procedures (Intuitive Surgical, Sunnyvale, CA, USA). After reviewing primary, adjuvant and salvage treatment history, preoperative $^{68}$Ga-PSMA imaging and intra-operative anatomical findings, each surgeon either chose to perform a targeted lymph node dissection limited to the $^{68}$Ga-PSMA-detected lesions and any surrounding suspicious lymph nodes, a unilateral or bilateral extended template pelvic lymph node dissection (PLND) encompassing skeletonization of the internal iliac, obturator, external iliac and common iliac landing areas, or a combination of both. On review of the data, a bilateral template dissection for pelvic nodes had been performed in the subgroup of patients who had no previous PLND and in whom the PSA recurrence ocurred early (i.e. within ~3 years of primary treatment). A targeted node dissection or unilateral template dissection had been performed in those patients with previous bilateral PLND or a long time interval between primary treatment and relapse. Histopathological evaluation of specimens was performed as per routine pathology protocols, with both lymph nodes and surrounding fat embedded in paraffin blocks.

### Outcomes and PSA Monitoring Postoperatively

Baseline characteristics and imaging data were available for all patients. PSA doubling time and velocity were calculated based on a minimum of three PSA measurements before RASND. Complications were reported according to the Clavien–Dindo classification system [16]. Histopathological

**Fig. 1** $^{68}$Gallium-labelled prostate-specific membrane antigen ($^{68}$Ga-PSMA) positron-emission tomography (PET)/CT scan of a 52-year-old man prior to robot-assisted salvage node dissection (RASND). This patient had previously undergone primary radical prostatectomy, with Gleason 4 + 5 = 9 disease on histopathology, 6 years prior to RASND, and subsequent adjuvant pelvic radiotherapy. Two lesions were identified on the pre-RASND $^{68}$Ga-PSMA PET/CT scan and histology confirmed cancer in two out of 11 resected LNs, after the patient underwent a targeted lymph node dissection of the $^{68}$Ga-PSMA PET/CT lesions and surrounding suspicious tissue. The patients' preoperative PSA level was 0.22 ng/mL, and this became undetectable 6 weeks after RASND.




reports were analysed for nodal involvement with adenocarcinoma. PSA level was measured at 6 weeks post-RASND procedure. In patients who had undergone primary RP, treatment response to RASND was defined as 6-week PSA <0.2 ng/mL (broad definition) and PSA <0.05 ng/mL (strict definition). For patients who underwent primary radiotherapy, a 6-week PSA level <post-radiotherapy nadir defined success. A subsequent PSA rise above 0.2 ng/mL for patients who had undergone primary RP, or PSA level above nadir for those who had undergone primary radiotherapy, represented subsequent post-RASND BCR. Data on clinical recurrence after RASND were based on clinically indicated follow-up bone scan or $^{68}$Ga-PSMA imaging. The timing and type of any additional systemic treatment after RASND were recorded. ADT was offered to patients if there was no treatment response to RASND and a rising PSA post-RASND or in the setting of post-RASND BCR and a rapidly rising PSA doubling time. BCR-free survival and clinical recurrence-free survival was calculated based on disease status at the time of most recent follow-up. Univariate analysis of predictors of broad- and strict-definition treatment response was performed using binary logistic regression.

## Results

### Baseline Characteristics

The characteristics of the 35 patients included in the analysis are summarized in Table 1. The median (interquartile range [IQR]) age at RASND was 67 (63–71) years and the median (IQR) time from primary treatment was 61.3 (20.5–90.9) months. The median (IQR) pre-RASND PSA level, PSA doubling time and PSA velocity were 2.2 (0.5–5.6) ng/mL, 7.4 (5.4–17.1) months and 1.3 (0.2–4.5) ng/mL/year, respectively. All the patients had undergone primary treatment with curative intent by RP ($n$ = 28, 80%), or radiotherapy ($n$ = 7, 20%). Of the 28 patients who underwent RP, 23 (82%) underwent PLND at the time of RP, with three pN1 cases

**Table 1** Baseline characteristics ($N$ = 35).

| Characteristic | Median (IQR) |
|---|---|
| Age at RASND, years | 67 (63–71) |
| Months from primary treatment to RASND | 61.3 (20.5–90.9) |
| PSA at diagnosis, ng/mL | 8.1 (5.1–12) |
| PSA nadir after primary radiotherapy, ng/mL ($n$ = 7) | 0.2 (0–1) |
| Pre-RASND PSA kinetics | |
| PSA at RASND, ng/mL | 2.2 (0.5–5.6) |
| PSA doubling time, months | 7.4 (5.4–17.1) |
| PSA velocity, ng/mL per year | 1.3 (0.2–4.5) |
| **Characteristic** | ***n* (%)** |
| Biopsy type | |
| TRUS | 29 (82.9) |
| Transperineal | 6 (17.1) |
| Biopsy Gleason sum | |
| 3 + 4 (ISUP Grade Group 2) | 6 (17.1) |
| 4 + 3 (ISUP Grade Group 3) | 9 (25.7) |
| 4 + 4 (ISUP Grade Group 4) | 6 (17.1) |
| 4 + 5 or 5 + 4 (ISUP Grade Group 5) | 14 (40) |
| Primary treatment | |
| Open prostatectomy | 10 (28.6) |
| Robot-assisted prostatectomy | 17 (48.6) |
| Laparoscopic prostatectomy | 1 (2.9) |
| HDR brachytherapy | 4 (11.4) |
| LDR brachytherapy | 1 (2.9) |
| External beam radiotherapy | 1 (2.9) |
| HDR + external beam radiotherapy | 1 (2.9) |
| pT stage at RP ($n$ = 28) | |
| pT2 | 4 (14.3) |
| pT3 | 23 (82.1) |
| pT4 | 1 (2.9) |
| Pathological Gleason sum at RP ($n$ = 28) | |
| 3 + 4 (ISUP Grade Group 2) | 3 (10.7) |
| 4 + 3 (ISUP Grade Group 3) | 7 (25) |
| 4 + 4 (ISUP Grade Group 4) | 1 (3.6) |
| 4 + 5 or 5 + 4 (ISUP Grade Group 5) | 17 (60.7) |
| Positive surgical margins at RP ($n$ = 28) | 6 (21.4) |
| pN status at RP ($n$ = 28) | |
| pN0 | 20 (71.4) |
| pN1 | 3 (10.7) |
| pNx | 5 (17.9) |
| Radiotherapy after RP ($n$ = 28) | 14 (50) |
| Prostate focal therapy after radiotherapy ($n$ = 7) | 1 (14.3) |
| Hormone therapy after primary treatment | 16 (45.7) |

*IQR, interquartile range; HDR, high-dose-rate; ISUP, International Society of Urological Pathology; LDR, low-dose-rate; RASND, robot-assisted salvage node dissection; RP, radical prostatectomy.*

(11%). Regarding additional treatment after primary therapy, 14 patients (50% of RP cohort) received adjuvant/salvage whole-pelvis radiotherapy, 16 patients (46% of total cohort) received ADT and one patient (14% of radiotherapy cohort) had salvage irreversible electroporation focal therapy to the prostate.

## Preoperative $^{68}$Ga-PSMA Imaging and Operative Dissection Technique

A total of 58 pelvic lesions were detected on preoperative $^{68}$Ga-PSMA imaging, with the majority of patients having 1–2 lesions (30 patients, 86%) confined to one side of the pelvis (31 patients, 89%; Table 2). Figure 2 represents the

**Table 2** $^{68}$Ga-PSMA pre-robot-assisted salvage node dissection imaging ($N$ = 35).

| Variable | *n* (%) |
|---|---|
| Number of positive $^{68}$Ga-PSMA sites per patient | |
| 1 | 20 (57.1) |
| 2 | 10 (28.6) |
| 3 | 3 (8.6) |
| 4 | 1 (2.9) |
| 5 | 1 (2.9) |
| Unilaterality of positive lesions on $^{68}$Ga-PSMA | |
| Unilateral/single midline | 31 (88.6) |
| Bilateral | 4 (11.4) |
| Location of positive lesions on $^{68}$Ga-PSMA ($n$ = 58) | |
| Pelvic | |
| Common iliac | 7 (12.1) |
| External iliac | 19 (32.8) |
| Obturator | 10 (17.2) |
| Internal iliac | 17 (29.3) |
| Perivesical | 1 (1.7) |
| Pre-sacral/para-rectal | 4 (6.9) |
| **Variable** | **Median (IQR)** |
| Maximum dimension per lesion, mm | 8 (5–11) |
| $SUV_{max}$ per lesion | 5.3 (4–7.7) |

*$^{68}$Ga-PSMA, $^{68}$gallium-labelled prostate-specific membrane antigen; IQR, interquartile range; $SUV_{max}$, maximum standardized uptake value.*

distribution of pelvic lesions on $^{68}$Ga-PSMA PET/CT, with a median (IQR) maximum dimension of the lesion of 8 (5–11) mm and maximum standardized uptake value of 5.3 (4–7.7). In all, 14 (40%), nine (26%), 10 (29%) and two patients (6%) underwent targeted dissections, unilateral extended template dissections, bilateral extended template dissections, or a combination of unilateral extended template and contralateral-targeted dissections, respectively (Table 3).

## Safety Outcomes

Eight patients (23%) experienced complications, all Clavien–Dindo grade ≤2, as summarized in Table 3. No intra-operative complications were noted.

## Robot-Assisted Salvage Node Dissection Procedure and Oncological Outcomes

The RASND procedure and oncological follow-up data are summarized in Tables 3 and 4, respectively. A total of 372 nodes were excised with a median (IQR) of 3 (1.8–6.3), 9 (8–14) and 17 (13.8–28.8) nodes for patients undergoing targeted, unilateral and bilateral dissections, respectively. A total of 32 patients (91%) had positive histopathology, with a total of 87 LNM and a median (IQR) of 2 (1-3) LNM per patient. The characteristics of the three patients with negative histopathology after RASND are shown in Table S1.

The median (IQR) follow-up was 12 (7.3–18.2) months. Treatment response was seen in 15 (43%) and 11 patients (31%) using the broad and strict definitions, respectively. The

**Fig. 2** $^{68}$Ga-PSMA pre-RASND lesion distribution (*N* = 58). Median (interquartile range [IQR]) maximum dimension of 8 (5–11) mm and median (IQR) maximum standardized uptake value ($SUV_{max}$) 5.3 (4–7.7) for each lesion.

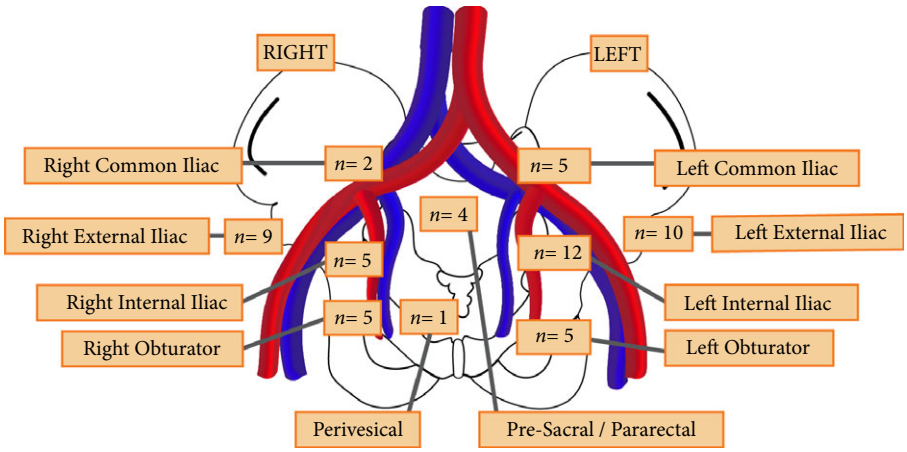



**Table 3** Robot-assisted salvage node dissection procedure data and complications (*N* = 35).

| Variable | |
|---|---|
| Type of RASND, *n* (%) | |
| Targeted pelvic dissection | 14 (40) |
| Unilateral extended pelvic template dissection | 9 (25.7) |
| Bilateral extended pelvic template dissection | 10 (28.6) |
| Unilateral extended pelvic template and contralateral targeted pelvic dissection | 2 (5.7) |
| Number of lymph nodes removed at RASND | |
| Total | 372 |
| Per-patient, median (IQR) | 9 (3–14) |
| Median (IQR) for targeted dissections | 3 (1.8–6.3) |
| Median (IQR) for unilateral dissections | 9 (8–14) |
| Median (IQR) for bilateral dissections | 17 (13.8–28.8) |
| Patients with positive nodes at RASND, *n* (%) | 32 (91.4) |
| No. of positive lymph nodes at RASND | |
| Total | 87 |
| Per patient median (IQR) | 2 (1–3) |
| Location of positive nodes on RASND per patient, *n* (%) | |
| Pelvic unilateral/single midline | 28 (80) |
| Pelvic bilateral | 4 (11.4) |
| Negative RASND | 3 (8.6) |
| Patients with postoperative complications, *n* (%) | 8 (22.9) |
| Specific complications | |
| Mild lymphoedema | 2 (5.7) |
| Temporary neuropraxia | 2 (5.7) |
| Temporary groin pain/lower limb pain | 2 (5.7) |
| Cardiac arrhythmia | 1 (2.9) |
| Pulmonary embolism | 1 (2.9) |
| Clavien–Dindo grade of complications (*n* = 8) | |
| Clavien–Dindo Grade 1 | 5 (62.5) |
| Clavien–Dindo Grade 2 | 3 (37.5) |
| Clavien–Dindo Grade 3–5 | 0 (0) |

**Table 4** Oncological follow-up (*N* = 35).

| | |
|---|---|
| Treatment response to RASND | |
| Entire cohort, *n* (%) | |
| Strict definition or radiotherapy definition at 6 weeks | 11 (31.4) |
| Broad definition or radiotherapy definition at 6 weeks | 15 (42.9) |
| Bilateral template dissection cohort (*n* = 10) | |
| Strict definition or radiotherapy definition at 6 weeks, *n* (%) | 8 (80.0) |
| Broad definition or radiotherapy definition at 6 weeks, *n* (%) | 9 (90.0) |
| Unilateral template dissection cohort (*n* = 9) | |
| Strict definition or radiotherapy definition at 6 weeks, *n* (%) | 1 (11.1) |
| Broad definition or radiotherapy definition at 6 weeks, *n* (%) | 3 (33.3) |
| Targeted dissection cohort (*n* = 14) | |
| Strict definition or radiotherapy definition at 6 weeks, *n* (%) | 2 (14.3) |
| Broad definition or radiotherapy definition at 6 weeks, *n* (%) | 3 (21.4) |
| Unilateral template and contralateral targeted dissection cohort (*n* = 2) | |
| Strict definition or radiotherapy definition at 6 weeks, *n* (%) | 0 (0) |
| Broad definition or radiotherapy definition at 6 weeks, *n* (%) | 0 (0) |
| Median (IQR) follow-up, months | |
| All patients post-RASND | 12.0 (7.3–18.2) |
| Median (IQR) PSA 6 weeks post-RASND | 0.4 (0.1–1.2) |
| BCR-free survival, *n* (%) | 8 (22.9) |
| Median (IQR) months to biochemical failure after initial 6-week PSA response | |
| Strict definition or radiotherapy definition, *n* = 6 | 5.4 (1.7–11.8) |
| Broad definition or radiotherapy definition median, *n* = 7 | 3.4 (1.8–10.5) |
| Patients with one or more sites of clinical progression, *n* (%) | 12 (34.3) |
| Clinical progression by site, *n* (%) | |
| Nodes | 11 (73.3) |
| Bones | 3 (20) |
| Visceral | 1 (6.7) |
| Median (IQR) months to clinical progression (*n* = 14) | 12 (6.2–16.1) |
| Additional treatment/s after RASND, *n* (%) | 14 (40) |
| Type of additional treatment commencement after RASND, *n* (%) | |
| Hormones | 12 (75) |
| Chemotherapy | 2 (12.5) |
| Radiotherapy | 2 (12.5) |
| Median (IQR) months to additional treatment (*n* = 16) | 8.2 (2–11.5) |

*BCR, biochemical recurrence; IQR, interquartile range; HDR, high-dose-rate; LDR, low-dose-rate; RASND, robot-assisted salvage node dissection.*

BCR-free survival rate at a median follow-up of 12 months was 23% for the entire cohort. In those with initial treatment response, the median (IQR) times to BCR were 3.3 (1.8–10.5) months and 5.4 (1.7–11.8) months using the broad and strict definitions of initial treatment response, respectively. Four patients (11%) had an undetectable PSA at the end of the study follow-up, with a median (IQR) follow-up for this group of 5.7 (2.3–22.3) months. Clinical progression occurred in 12 patients (34%), at a median (IQR) time to progression of 12 (6.2–16.1) months, two of whom had an initial treatment response (strict definition). Of these

12 patients, 11 (92%), three (25%) and one (8%) had new node, bone and visceral metastases, respectively.

In the subset of 10 patients who underwent bilateral extended template RASND, nine (90%) and eight (80%) had a treatment response based on the broad and strict definitions, respectively. The BCR-free survival rate for this subset of patients was 40% at a median (IQR) follow-up of 8 (4.6–16.9) months. One patient (3%), who had undergone bilateral extended template RASND, had a clinical pelvic node relapse in the right perivesical/retropubic region detected at 19 months after RASND. In the subset of eight patients who had a treatment response according to strict definition criteria (PSA <0.05 ng/mL) and a time from primary to salvage treatment of >36 months, BCR-free survival was 50% at a median (IQR) follow-up of 8.5 (2.3–14.3) months. Of this subgroup of eight patients, five (63%) had undergone previous primary RP, with two undergoing PLND and four receiving adjuvant or salvage radiotherapy, three patients (38%) had undergone previous primary radiotherapy, five patients (63%) had previous adjuvant or salvage short-course ADT treatment, and five patients received a bilateral template dissection at time of RASND (63%).

On univariate binary logistic regression, the only significant predictor for treatment response was type of RASND being a bilateral template dissection (broad-definition treatment response analysis: odds ratio 28.5, 95% CI 4.17–584.92, $P < 0.01$; strict-definition treatment response analysis: odds ratio 29.33, 95% CI 4.89–277.37, $P < 0.01$). The remaining univariate analysis is shown in Table 5.

### Post-RASND Therapy

After RASND, 14 patients (40%) were commenced on further treatment at a median (IQR) time of 8.2 (2–11.5) months (Table 4) and 12 (75%), two (12.5%) and two patients (12.5%) initiated ADT, radiotherapy and chemotherapy, respectively.

## Discussion

The development of novel imaging techniques, which identify oligometastatic disease at an earlier stage than conventional imaging in patients with BCR after radical treatment, has led to the new clinical question of whether metastases-directed therapy might delay the morbidity of systemic therapy, improve overall QoL and even improve survival in selected patients.

In the present study, we report modest success in terms of treatment response rate (depending on the definition used: 43% broad definition, 31% strict definition), BCR-free survival rate (23%), clinical recurrence-free survival rate (66%) and systemic therapy-free rate (60%) at a median follow-up of 12 months. For patients in whom the time from primary therapy to RASND was >36 months and for whom successful treatment response was achieved according to strict criteria (PSA <0.05 ng/mL post-RASND), 50% were BCR-free at a median follow-up of 9 months. Of patients who underwent bilateral extended template RASND, 40% were BCR-free at a median follow-up of 8 months.

While these findings are hypothesis-generating rather than conclusive, it suggests that certain preoperative and treatment factors may predict the likelihood of success with RASND. Factors that should be studied further include time from primary treatment, absolute PSA level and PSA kinetics at time of treatment selection, number of positive lesions on imaging, stability of disease on imaging over time and extent of surgery (limited PLND vs extended template PLND vs targeted 'lumpectomy'; unilateral vs bilateral template

**Table 5** Univariate binary logistic regression analysis for predictors of treatment response, according to broad (PSA <0.2 ng/mL) and strict (PSA <0.05 ng/mL) definitions, in 35 patients undergoing robot-assisted salvage node dissection.

| | Broad-defninition treatment response | | Strict-definition treatment response | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | *P* | Odds ratio (95% CI) | *P* |
| Type of RASND | | | | |
| Bilateral template dissection | 28.50 (4.17–584.92) | <0.01 | 29.33 (4.89–277.37) | <0.01 |
| Any other dissection | Reference | – | Reference | – |
| PSA | 0.97 (0.81–1.14) | 0.72 | 1.02 (0.85–1.20) | 0.81 |
| PSA doubling time | | | | |
| <6 months | Reference | – | Reference | – |
| ≥6 months | 0.38 (0.09–1.57) | 0.18 | 0.28 (0.06–1.23) | 0.09 |
| Biopsy Gleason score sum | | | | |
| ≤7 (ISUP Grade Group 1–3) | Reference | – | Reference | – |
| 8–10 (ISUP Grade Group 4–5) | 0.76 (0.19–2.97) | 0.69 | 0.86 (0.20–3.73) | 0.83 |
| Time since primary treatment | | | | |
| <36 months | Reference | – | Reference | – |
| ≥36 months | 0.76 (0.19–2.97) | 0.69 | 2.67 (0.60–14.51) | 0.20 |
| Number of $^{68}$Ga-PSMA lesions | 0.78 (0.33–1.59) | 0.49 | 0.83 (0.32–1.75) | 0.63 |

*$^{68}$Ga-PSMA, $^{68}$gallium-labelled prostate-specific membrane antigen; ISUP, International Society of Urological Pathology; RASND, robot-assisted salvage node dissection.*

dissection) as shown in Table 5. Longer follow-up and larger sample sizes may allow further identification of factors predicting success with RASND.

The present study adds to the scarce literature available on $^{68}$Ga-PSMA-guided-SLND and, to our knowledge, is the second study reporting on the feasibility and early oncological results of RASND, after the study by Montorsi et al. [17–21]. Recently, Porres et al. [18] reported on the largest cohort of patients who underwent open-SLND based on F-18 fluoroethylcholine ($^{18}$FEC)-detected (38 patients) and $^{68}$Ga-PSMA PET/CT-detected (49 patients) oligometastatic nodal recurrence. They reported complete treatment response in 27.5% of patients based on a post-SLND PSA level <0.2 ng/mL, with 61/87 (70%) patients having positive histopathology. The 3-year BCR-free survival, clinical recurrence-free survival and systemic therapy-free survival rates were 27%, 63% and 41%, respectively, for the entire cohort, with no complications of Clavien–Dindo grade >3. In comparison, the first RASND series reported by Montorsi et al. [17] showed the results of 13 patients who underwent $^{68}$Ga-PSMA-guided RASND and three patients who underwent choline-guided RASND for node-only recurrence after RP, reporting a 33% treatment response, as measured by 40-day PSA <0.2 ng/mL, and 11/16 patients (69%) having positive histopathology at RASND [17]. In that cohort, four intra-operative complications (25%) and five postoperative Clavien–Dindo grade <3 complications (31%) were noted. Long-term survival data are lacking regarding $^{68}$Ga-PSMA-directed SLND for oligometastatic nodal recurrence, but Suardi et al. [22,23] reported 8-year clinical recurrence-free survival of 38% and PCa-specific mortality-free rates of 81% in a carefully selected cohort of patients at low risk of PCa-specific mortality undergoing open choline-guided SLND.

The present study has several important differences from the initial studies reporting on $^{68}$Ga-PSMA-guided SLND. Firstly, it includes only patients who underwent $^{68}$Ga-PSMA-guided RASND procedures, with a cohort more than twice the size of that reported by Montorsi et al. [17]. Secondly, it includes patients who underwent both RP or radiotherapy as primary therapy, thus increasing the generalizability of the results. Thirdy, the median follow-up was longer than that of the first report on RASND. Finally, we performed our analysis using both broad and strict definitions of treatment response, given that a lower post-treatment PSA is a strong predictor of BCR-free survival after primary treatment [17,18,21,24]. We show RASND to be a safe and feasible operation in the hands of experienced robot-assisted surgeons, with no patients in our cohort experiencing intra-operative complications or postoperative Clavien–Dindo grade ≥3 complications, even in the setting of previous pelvic radiotherapy. The majority of patients will not achieve cure, but a minority may achieve prolonged progression-free survival and thus benefit from delaying or avoiding the morbidity of systemic therapy.

Yossepowitch [25] posed three questions when considering the use of SLND for PCa relapse: (i) What is the clinical indication? (ii) What is the clinical benefit? and (iii) What should be the extent of dissection? With a number of large cohort retrospective studies showing that patients with metastatic PCa with low-volume nodal disease have longer survival compared with patients with more extensive node, bone or visceral dissemination, it would appear that these patients might have a more favourable cancer phenotype [10–14]. Subsequently, SLND has been proposed to be a treatment option for this group, relying heavily on the accuracy of imaging detection. Selection of patients in most SLND cohorts has been previously limited to choline-based imaging [9,15]. $^{68}$Ga-PSMA PET/CT has superior sensitivity and specificity for node and bone metastases detection compared with other restaging methods (e.g. CT, bone scintigraphy and MRI) hence this novel technique has been used to select patients for SLND in recent case series [7,19–21,26]. A number of selection and treatment factors may improve outcomes. Firstly, we found that the median time to BCR after RASND was 3–5 months. Perhaps a period of observation of 9–12 months to assess PSA velocity and then repeat the $^{68}$Ga-PSMA PET/CT may enable identification and exclusion of those patients in whom the PSMA-positive node represents 'the tip of the iceberg' and who would have experienced recurrence after RASND if it had been performed early. Secondly, despite variation in the extent of surgical dissection, 58 pre-RASND lesions were detected on $^{68}$Ga-PSMA PET/CT, compared with 87 LNM on histopathology, suggesting that although the sensitivity was improved compared with standard CT, it was still sub-optimal at 67% (58/87 on a 'per-node'-based analysis in this cohort; furthermore this may differ from the true 'per-patient' and 'per-node' sensitivity because patients with a 'negative' $^{68}$Ga-PSMA did not undergo RASND). These findings are in keeping with the moderate sensitivity of $^{68}$Ga-PSMA PET/CT in detecting lymph node recurrence reported in a recent meta-analysis and a recent study at our institution [26,27]. Given this, as well as our univariate analysis of predictors of success, if RASND is being considered, an extended template for dissection should be justified to ensure coverage of both $^{68}$Ga-PSMA-detected lesions and additional micro-metastatic deposits below the threshold of current imaging detection. Thirdly, $^{68}$Ga-PSMA PET/CT also carries a risk of false-positives, although a lower risk than choline-based PET/CT; three patients in the present cohort had negative histopathology after RASND, all of whom had targeted rather than template dissections (Table 5). It is unknown whether these represent false-positives on $^{68}$Ga-PSMA PET/CT, nodes missed at histopathology or nodes missed at surgery.

Although PSA response and avoidance of systemic therapy have been commonly reported endpoints in SLND studies, further research into long-term survival, QoL and cost–benefit

analysis endpoints are required to critically assess the potential clinical benefits of RASND for PCa nodal relapse before it can be recommended in routine clinical practice [25]. An adequately powered, multicentre, prospective, randomized clinical trial would be the optimum design to determine the utility of this therapy.

At present, there is variability amongst urologists in terms of lymph node dissection utilization and extent at time of primary RP [28]. Similarly, although the role of staging has been established, the therapeutic benefit of lymph node dissection in the primary setting remains controversial [29]. In the salvage setting it is even more complicated to delineate the role of targeted vs extended template dissections, when looking at existing studies, given the significant variability in primary dissection indication and extent, previous radiotherapy to the pelvis and the accuracy of restaging imaging techniques used [25].

The present study has several limitations. It is a retrospective case series, which creates potential for selection and measurement bias, although none was identified and all data collection/analysis was performed by researchers independently of the treating surgeons. The sample size was small and follow-up was short, which is unavoidable given that this is a novel imaging technique and treatment approach. Short follow-up precludes analysis of the most important outcomes: cancer-specific survival, overall survival and QoL. The small sample size meant that it was not feasible to perform a multivariate analysis to identify predictors of treatment response, BCR-free survival and clinical recurrence-free survival, and instead only a limited univariate analysis was performed.

There were slight differences in the imaging protocol used at each centre [4,5]. Despite this, it is our opinion that these differences should not have materially affected the validity of the results and, in fact, the high level of $^{68}$Ga-PSMA PET/CT experience of both participating imaging units and the experience of the robotic surgeons were relative strengths of the study [5,26,30]. There was variance between surgical dissection extent, and subsequently lower nodal yield in some patients. Although the treatment response results appeared better in the patients who underwent bilateral extended template dissections, it is difficult to comment on whether surgical technique played a significant role in oncological outcomes given inherent selection biases resulting from factors influencing treatment choice, small patient numbers and the inability to adjust for these factors via multivariate regression analysis.

Finally, the present study lacks a comparison group, which makes it impossible to draw conclusions regarding treatment benefit when compared with standard care. This limitation will be somewhat addressed by the currently accruing phase II randomized STOMP trial comparing surveillance to metastases-directed therapy (surgery or radiotherapy) for oligometastatic recurrent disease detected by choline-PET/CT [31]. Primary endpoints of ADT-free survival, and secondary endpoints of safety, QoL and progression-free survival will help to further characterize the role of SLND in the oligometastatic patient population. Nevertheless, prospective randomized studies that use newer $^{68}$Ga-PSMA imaging to guide therapy are needed, with long-term survival, QoL and cost–benefit analysis endpoints.

Although RASND appears safe and feasible, fewer than half of the patients in our cohort had a treatment response to RASND, and fewer than one in four patients had BCR-free survival at a median of 12 months' follow-up, therefore we advise RASND uptake only in the setting of a clinical trial at present, with particular caution with regard to patient selection and preoperative counselling about the likelihood of long-term remission. Further studies with a larger sample size and longer follow-up are needed to assess potential QoL and mortality benefits, and to define which factors (if any) predict benefit from RASND. Given $^{68}$Ga-PSMA imaging underestimates the extent of metastatic disease, $^{68}$Ga-PSMA-guided excision/radiotherapy directed only to positive nodes without template lymphadenectomy/regional radiotherapy will be unlikely to provide a durable treatment response.

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## Conflicts of Interest

None declared.

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Abbreviations: $^{68}$Ga-PSMA, $^{68}$gallium-labelled prostate-specific membrane antigen; PET, positron emission tomography; RASND, robot-assisted salvage node dissection; BCR, biochemical recurrence; LNM, lymph node metastases; PCa, prostate cancer; QoL, quality of life; SLND, salvage lymph node dissection; RP, radical prostatectomy; ADT, androgen deprivation therapy; PLND, pelvic lymph node dissection; IQR, interquartile range.

## Supporting Information

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

**Table S1.** Characteristics of patients with negative histopathology at RASND ($n$ = 3).

 