# OUTCOMES OF SALVAGE LYMPH NODE DISSECTION FOR PROSTATE CANCER WITH CLINICAL NODAL RELAPSE: RESULTS OF A MULTICENTRIC, RETROSPECTIVE STUDY

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## ABSTRACT

Introduction: Salvage lymph node dissection (sLND) is a treatment option for prostate cancer (PCa) patients with nodal recurrence after radical therapy to delay tumour progression and hormonal treatment. We evaluated the outcomes in terms of biochemical recurrence (BCR), clinical regression, and cancer specific survival (CSS) in a large, multicentric series of patients treated with sLND for nodal recurrence of PCa.

Methods: We retrospectively reviewed the records of 106 consecutive patients with BCR of PCa after radical treatment who underwent sLND between 2007 and 2013 at three tertiary centres. BCR was defined as prostate-specific antigen (PSA) >0.2 ng/mL. Clinical recurrence (CR) was defined as a positive imaging study or biopsy for metastasis after sLND. Kaplan–Meier curves calculated BCR-free survival (BFS), CR-free survival (CRS), and CSS. Cox regression analyses were performed to identify predictors of CR.

Results: Median number of nodes removed at sLND was 21.7, with a median of three positive nodes. Immediate biochemical response after surgery was achieved in 50.9% of patients. At a median follow-up of 22.5 months, biochemical failure and CR were experienced by 67.9% and 40.5% of patients, respectively. At 2 years, BFS, CRS, and CSS were 25%, 52%, and 92%, respectively. Castrate-resistant prostate cancer (CRPC) status, PSA level at sLND, and presence of biochemical failure after sLND were significantly associated with CR after surgery.

Conclusions: sLND represents a valid treatment option for selected patients with nodal recurrences, achieving a CR-free status in more than half of patients at 2 years. Patients with CRPC status or high PSA values might not be the best candidates for a sLND.

Keywords: Salvage lymph node dissection (sLND), prostate cancer (PCa), biochemical recurrence (BCR), choline positron emission tomography (PET).

## INTRODUCTION

Although radical treatments for localised prostate cancer (PCa) achieve excellent cancer control rates,[1] around 40% of patients develop a biochemical recurrence (BCR),[1,2] which can be associated with local or systemic recurrence of PCa. These individuals, who are at higher risk of death from PCa,[3] can have nodal metastases as the only sites of recurrent disease.[4] Traditionally, such patients would be considered as harbouring systemic disease, and thus be managed with hormone replacement therapy (HRT).[5] Recent evidence, however, supports the effectiveness of salvage lymph node dissection (sLND) as a treatment option to delay tumour progression and thus postpone

HRT in patients with disease relapse limited to lymph nodes (LN).[6] In this light, $^{11}$C-choline positron emission tomography (PET)/computed tomography (CT) currently plays an essential role in the early detection of nodal metastases to correctly select patients suitable for sLND.[7,8]

Previous studies have reported that although most patients inevitably progress to BCR after sLND, roughly 40% do not experience any further clinical recurrence (CR) even at long-term follow-up.[9,10] These are promising results; however, the feasibility of sLND in clinical practice remains limited by the lack of data concerning oncologic and surgical outcomes of this pioneering surgery. The aim of our study is to report the outcomes in terms of BCR, CR, and cancer-specific survival (CSS) in a multicentric series of patients treated with sLND for nodal recurrence of PCa. To our knowledge, this is the largest series published to date.

## METHODS

### Patient Population

After institutional review board approval, we retrospectively reviewed the records of 106 consecutive patients with BCR of PCa after radical treatment (radical prostatectomy [RP], N=102; external beam radiation therapy [EBRT], N=3; brachytherapy, N=2) who underwent $^{11}$C-choline PET/CT and sLND between 2007 and 2013 at three tertiary centres. BCR was considered to be a rise of prostate-specific antigen (PSA) to >0.2 ng/mL after RP and a PSA level >2 ng/mL higher than the PSA nadir value after radiotherapy.[11] Castrate-resistant prostate cancer (CRPC) patients were defined as patients with <1.7 nmol/L serum testosterone and biochemical progression.[5] All but six patients (who only had findings of enlarged nodes in CT scans) showed pathological uptake in at least one LN in PET/CT imaging. Pelvic and/or retroperitoneal sLND was performed according to the location of positive nodes at imaging. Patients referred for sLND had BCR after radical treatment for PCa, with evidence of nodal disease only at imaging. Preoperative imaging modalities were as previously described.[8]

### Surgical Procedure and Follow-Up

Surgical dissection was not restricted to the PET/CT targeted area, but was extended to neighbouring regions according to surgical preference. Given the current unavailability of a recommended surgical template, no standardised surgical approach could be adopted. An open approach was used in all but two patients, in whom laparoscopic sLND was performed. After sLND, surgical specimens were processed according to standard pathology protocols and evaluated by a dedicated uro-pathologist in each institution. Use of any therapy after surgery, including HRT, was decided on a case-by-case basis following multidisciplinary consultation. Follow-up consisted of periodical PSA testing and clinical visits. Postoperative imaging, including CT, magnetic resonance imaging, bone scintigraphy, or $^{11}$C-choline PET/CT was performed in cases of BCR after sLND. Complications were reported according to the modified Clavien–Dindo classification.[12]

### Statistical Analysis

Descriptive statistics were used to explore perioperative and pathologic variables. Primary outcomes were time to biochemical failure, CR, and cancer-specific mortality. Kaplan–Meier survival curves and life tables were calculated for each outcome. Biochemical failure comprised both patients with BCR after the initial PSA response (<0.2 ng/mL) following sLND, and those not attaining a PSA <0.2 ng/mL (immediate BCR). Biochemical response (BR) included patients attaining a PSA <0.2 ng/mL. CR was defined as a positive imaging study or biopsy for metastasis after sLND. Univariable and multivariable Cox regression analyses were performed to identify predictors of CR. Statistical significance was claimed for $p<0.05$. All statistical analyses were performed with SPSS v.20 (IBM, New York, USA).

## RESULTS

### Baseline Characteristics and Pathologic Outcomes

Table 1 depicts the baseline characteristics of all patients included in the study, both at the time of primary treatment and at sLND. At sLND, median patient age was 65 years (range, 48–81), with a median PSA of 3.1 ng/mL (range, 0.2–47). Mean time from PET/CT to sLND was 1.5 months (SD±0.7). Overall, PET/CT detected a median of 1.5 positive nodes per patient. Data concerning PET/CT accuracy were previously reported.[8] Adjuvant and salvage therapies before sLND were adopted in a large number of patients. Nineteen patients (18%) already possessed CRPC status before undergoing sLND. The median number of nodes removed was 21.7 (range, 2–78), with a

median of three positive nodes on final histology (range, 0–33). sLND found no positive nodes in 16 patients (15%).

## Patient Outcomes, Survival, and Complications

Surgical outcomes are shown in Table 2. BR immediately after surgery was achieved by 50.9% of patients. At last follow-up, biochemical failure was noted in 67.9% of cases, with a mean time of 19 months. CR was experienced by 40.5% of patients, mainly at nodal or bone level, with a mean time of 38 months. At a median follow-up of 22.5 months, only five patients of our series died from PCa. Kaplan–Meier survival curves for BCR-free survival (BFS), CR-free survival (CRS), and CSS are shown in Figure 1. At 2 years, BFS, CRS, and CSS were 25%, 52%, and 92%, respectively. Thirty-six patients (33.9%) experienced postoperative complications, of which only 10 (9.4%) were graded as Clavien III-IV (Table 2).

## Univariable and Multivariable Cox Regression Models Predicting Clinical Progression

In univariable Cox regression models considering the main preoperative and postoperative variables, CRPC status, PSA level at sLND, and presence of biochemical failure after sLND were significantly associated with CR after surgery (Table 3). In multivariable analyses, all of these variables represented independent predictors of CR (all $p<0.02$).

**Table 1: Baseline patient characteristics.**

| Variable | All patients (N=106) | Radical prostatectomy (N=101) | Radiation therapy or brachytherapy (N=5) |
|---|---|---|---|
| **Patient characteristics at time of primary treatment** | | | |
| Age (years), mean±SD<br>Age (years), median (range) | 59.4±6.8<br>59 (46–75) | 59.5±6.8<br>59 (46–75) | 57.6±5.4<br>55 (53–66) |
| Years considered | 1993–2013 | 1993–2013 | 2001–2011 |
| PSA, ng/mL, mean±SD<br>PSA, ng/mL, median (range) | 11.0±8.4<br>8.6 (2.0–44.6) | 11.0±8.1<br>8.7 (2.5–44.6) | 12.0±13.1<br>4.6 (2.0–33.4) |
| GS<br>• ≤6, n (%)<br>• 7, n (%)<br>• 8–10, n (%) | <br>4 (3.8)<br>60 (56.6)<br>42 (39.6) | Pathologic GS<br>3 (3.0)<br>58 (57.4)<br>40 (39.6) | Bioptic GS<br>1 (20.0)<br>2 (40.0)<br>2 (40.0) |
| Stage at radical prostatectomy<br>• pT3, n (%)<br>• pNx, n (%)<br>• pN1, n (%) | <br>NA<br>NA<br>NA | Pathologic stage<br>65 (64.3)<br>23 (22.7)<br>7 (6.9) | Clinical stage<br>1 (20)<br>NA<br>NA |
| Positive margins, n (%) | NA | 41 (45.1) | NA |
| Nodes removed, mean (range) | NA | 11.7 (2–45) | NA |
| Positive nodes, mean (range) | NA | 1.75 (1–4) | NA |
| Adjuvant therapies, n (%)<br>• RT<br>• HRT | <br>22 (20.7)<br>11 (10.3) | <br>22 (21.3)<br>10 (9.7) | <br>NA<br>1 (20) |
| Months to BCR, mean±SD<br>Months to BCR, median (range) | 40.4±37.4<br>31.0 (1–190) | 38.0±34.3<br>30.5 (1–190) | 81.8±66.3<br>99.0 (12–150) |
| **Patient characteristics at time of sLND** | | | |
| Age (years), mean±SD<br>Age (years), median (range) | 65.3±6.9<br>65.5 (48–81) | 64.3±7.0<br>65 (48–81) | 66.2±6.7<br>67 (56–75) |
| Years considered | 2007–2014 | 2007–2014 | 2013–2014 |
| Time from primary treatment to sLND (months), mean±SD<br>Time from primary treatment to sLND (months), median (range) | 70.2±49.4<br>59 (6–233) | 68.7±48.8<br>56 (6–233) | 101.8±55.6<br>106 (20–159) |
| Salvage therapies before sLND, n (%)<br>• RT<br>• HRT<br>• Chemotherapy + HRT | <br>53 (50)<br>22 (20.7)<br>8 (7.5) | <br>53 (52.4)<br>20 (19.8)<br>8 (7.9) | <br>NA<br>2 (40)<br>0 (0) |

**Table 1 continued.**

| Variable | All patients (N=106) | Radical prostatectomy (N=101) | Radiation therapy or brachytherapy (N=5) |
|---|---|---|---|
| PSA, ng/mL, mean±SD<br>PSA, ng/mL, median (range) | 3.1±5.0<br>1.0 (0.2–47) | 2.1±3.1<br>1.0 (0.1–17) | 2.5±1.7<br>1.4 (1.3–4.8) |
| CRPC, n (%) | 19 (17.8) | 16 (15.7) | 3 (60) |
| Positive nodes at PET/CT, mean±SD<br>Positive nodes at PET/CT, median (range) | 2.01±1.6<br>1.5 (0–9) | 1.99±1.6<br>1 (0–9) | 2.4±1.1<br>2 (1–4) |
| Positive locations at PET/CT, n (%)<br>• Pelvic only<br>• Retroperitoneal only<br>• Pelvic plus retroperitoneal<br>• Negative | <br>82 (77.3)<br>6 (5.6)<br>12 (11.3)<br>6 (5.6) | <br>78 (77.2)<br>5 (4.9)<br>12 (11.8)<br>6 (5.9) | <br>4 (80)<br>1 (20)<br>0 (0)<br>0 (0) |
| Nodes removed at sLND, mean±SD<br>Nodes removed at sLND, median (range) | 21.7±14.5<br>20.5 (2–78) | 20.5±12.8<br>18.0 (2–62) | 47.6±23.3<br>45 (24–78) |
| Positive nodes at sLND, mean±SD<br>Positive nodes at sLND, median (range) | 4.7±5.4<br>3 (0–33) | 4.4±4.5<br>3 (0–20) | 10.8±14.4<br>3 (0–33) |
| Positive locations at sLND, n (%)<br>• Pelvic only<br>• Retroperitoneal only<br>• Pelvic plus retroperitoneal<br>• Negative | <br>66 (62.2)<br>5 (4.7)<br>19 (17.9)<br>16 (15.1) | <br>65 (64.3)<br>4 (3.9)<br>19 (18.8)<br>14 (13.8) | <br>1 (20)<br>1 (20)<br>0 (0)<br>2 (40) |

sLND: salvage lymph node dissection; PET: positron emission tomography; CT: computed tomography; GS: Gleason score; pT3: tumour extends beyond the prostate; pNx: regional lymph nodes were not assessed; pN1: regional lymph nodes affected by tumour; BCR: biochemical recurrence; RT: radiotherapy; HRT: hormone replacement therapy; PSA: prostate-specific antigen; CRPC: castrate-resistant prostate cancer.

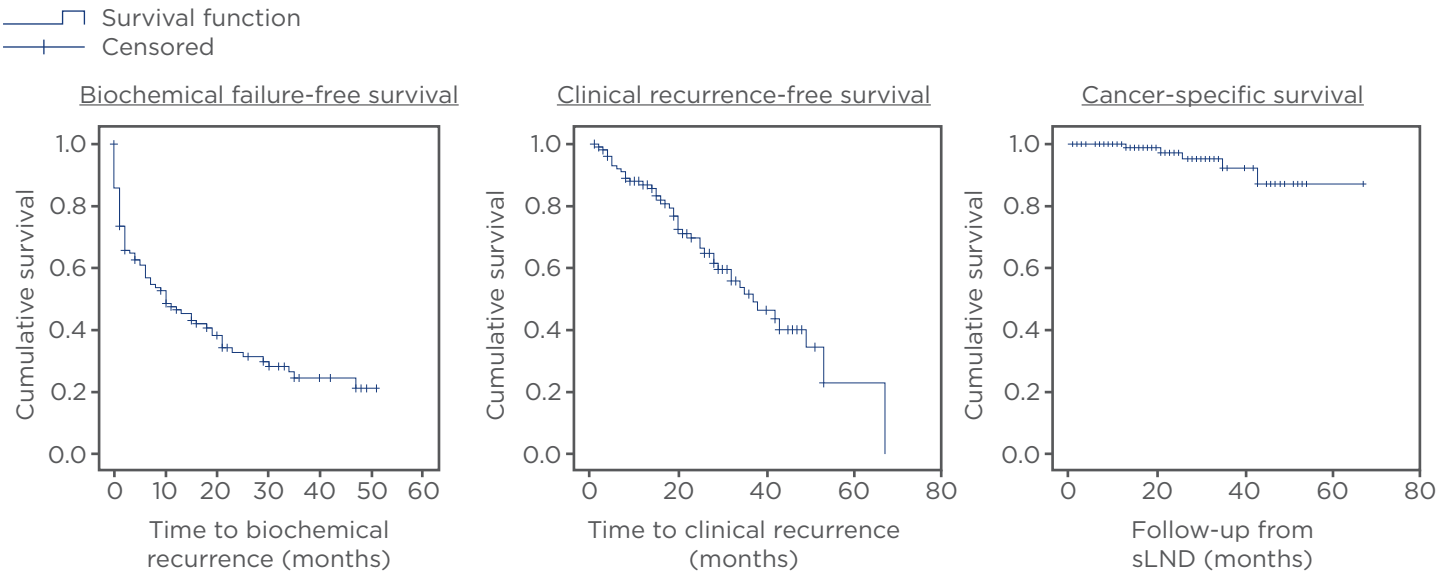


**Figure 1: Kaplan-Meier survival curves.**
sLND: salvage lymph node dissection.

## DISCUSSION

Recent advances in clinical imaging techniques, and in particular molecular imaging such as $^{11}$C-choline PET/CT, have allowed the identification of cases with oligometastatic nodal recurrence after radical therapy for PCa.[7,8] These are patients with presumed 'systemic' disease that is limited to the pelvic and/or retroperitoneal LNs. Traditionally, these these types of patients would have been

referred to HRT,[5] being at increased risk of death from PCa.[2] However, HRT is not a curative option and is burdened by non-negligible toxicity.[13] Moreover, many patients ultimately develop CRPC.[14]

In recent years, sLND has emerged as an appealing therapeutic alternative for this group of patients, showing favourable cancer-control outcomes in terms of delayed progression and postponement of HRT.[6,9-11,15-18] The rationale of this targeted surgery resides in the consideration that extended pelvic LN dissection at the time of radical prostatectomy is associated with more favourable survival rates in patients with low nodal disease burden, defined as up to two positive nodes.[6,11,19] In other words, nodal disease can still be considered regional in select cases. The question is whether limited nodal recurrence following local treatment with curative intent will be viewed in the same way. In other words, does sLND have curative potential, or at least therapeutic benefit as a cytoreductive measure?

Recent studies have analysed the outcomes of this controversial procedure. The first published large series of sLND was that of Rigatti et al.,[15] who analysed the data of 72 patients with BCR after RP associated with clinical nodal recurrence. Forty-one patients (57%) achieved a complete BR after sLND. In the entire cohort, the 5-year BFS, CRS, and CSS were 19%, 34%, and 75%, respectively.

**Table 2: Patient outcomes and complications.**

| Variable | All patients (N=106) |
|---|---|
| **Operative outcomes** | |
| Estimated blood loss (cc), mean±SD<br>Estimated blood loss (cc), median (range) | 395.3±434.3<br>250 (0–2700) |
| Length of hospital stay (days), mean±SD<br>Length of hospital stay (days), median (range) | 5.0±4.8<br>4.5 (0–31) |
| **Oncologic outcomes** | |
| Follow-up from primary treatment (months), mean±SD<br>Follow-up from primary treatment (months), median (range) | 95.9±50.6<br>86 (11–256) |
| Follow-up from sLND (months), mean±SD<br>Follow-up from sLND (months), median (range) | 25.7±15.1<br>22.5 (1–67) |
| Biochemical response immediately after sLND, n (%) | 54 (50.9) |
| Biochemical response at 22 months after sLND, n (%) | 34 (32.1) |
| Further treatments after sLND, alone or in combination, n (%)<br>• HRT (for at least a period of time)<br>• Chemotherapy<br>• RT on metastases | <br>71 (66.9)<br>13 (12.2)<br>12 (11.3) |
| Biochemical failure after sLND, n (%) | 72 (67.9) |
| Months to biochemical failure after sLND, mean (95% CI)* | 19.1 (15.0–23.1) |
| Clinical recurrence after sLND, n (%) | 43 (40.5) |
| Months to clinical recurrence after sLND, mean (95% CI)* | 38.1 (32.4–43.8) |
| Site of clinical recurrence, n (%)<br>• Local<br>• Nodal<br>• Bone<br>• Visceral | <br>4 (3.7)<br>24 (22.6)<br>16 (15.0)<br>2 (1.8) |
| Cancer-specific mortality, n (%) | 5 (4.7) |
| Months to cancer-specific mortality, mean (95% CI)* | 62.5 (58.7–66.3) |
| **Survival** | |
| Biochemical failure-free survival<br>• 2-years<br>• 4-years | <br>25%<br>22% |
| Clinical recurrence-free survival<br>• 2-years<br>• 4-years | <br>52%<br>25% |
| Cancer-specific survival<br>• 2-years<br>• 4-years | <br>92%<br>88% |

**Table 2 continued.**

| Variable | | All patients (N=106) |
|---|---|---|
| Complications | | |
| **Complication type** | **Clavien Grade** | **Overall, n (%)** |
| Lymphorrhoea | I | 11 (10.3) |
| Postoperative pain | I | 4 (3.7) |
| Pulmonary atelectasis | I | 1 (0.9) |
| Ileus | II | 1 (0.9) |
| Wound infection | II | 3 (2.7) |
| Pneumonia | II | 2 (1.8) |
| Pulmonary embolism | II | 1 (0.9) |
| Haemorrhage, with transfusions | II | 3 (2.7) |
| Lymphocele, requiring drainage | IIIa | 2 (1.8) |
| Haemorrhage, requiring embolisation | IIIa | 1 (0.9) |
| Wound dehiscence | IIIa | 1 (0.9) |
| Hydronephrosis, requiring ureteral stenting | IIIa | 2 (1.8) |
| Surgical reintervention | IIIb | 3 (2.7) |
| Rectovesical fistula | IIIb | 1 (0.9) |

*according to Kaplan–Meier survival estimates
RT: radiotherapy; HRT: hormone replacement therapy; sLND: salvage lymph node dissection; CI: confidence interval.

**Table 3: Cox regression models predicting CR after sLND.**

| Variable | Univariable | | Multivariable | |
|---|---|---|---|---|
| | HR (95%, CI) | p-value | HR (95%, CI) | p-value |
| **Time to BCR** | 1.00 (0.99–1.01) | 0.48 | - | - |
| **CRPC status** | 3.88 (1.04–14.49) | **0.04** | 32.4 (1.48–711.08) | **0.02** |
| **PSA at sLND (ng/mL)** | 1.26 (1.04–1.52) | **0.01** | 1.30 (1.04–1.62) | **0.01** |
| **Positive nodes, n** | 0.99 (0.93–1.07) | 0.97 | - | - |
| **Biochemical failure** | 6.48 (2.25–18.63) | **0.001** | 4.34 (1.26–14.96) | **0.02** |

BCR: biochemical recurrence; CRPC: castrate-resistant prostate cancer; PSA: prostate-specific antigen; sLND: salvage lymph node dissection; CI: confidence interval; HR: hazard ratio; CR: clinical regression.

In a recent update of this series, the same authors focussed on 59 patients with >5 years of follow-up. Complete BR was achieved in 35 patients (59.3%) after sLND. The estimated 8-year BFS, CRS, and CSS were 23%, 38%, and 81%, respectively.[9] Another report on sLND was published by Jilg et al.,[16] who evaluated the data of 52 patients with BCR after radical treatment associated with clinical nodal recurrence in PET/CT imaging. The authors excluded patients who received radiotherapy after primary treatment and before sLND. Adjuvant EBRT was administered following sLND in 27 cases (52%). Twenty-four patients (46%) had complete BR after surgery, and a 1-year BFS of 71.8%. In the entire cohort, the estimated 5-year CRS and CSS were 26% and 78%, respectively. Another series of sLND was recently published by Karnes et al.,[10] who analysed the data of 52 patients, 78.8% of whom had already undergone adjuvant or salvage therapy after RP. At a median follow-up of 20 months, 46.2% of patients had not received further treatments, 57.7% had PSA <0.2 ng/mL, and 34.6% were on HRT. Estimated 3-year BFS, CRS, and CSS were 45.5%, 46.9%, and 92.5%, respectively.

The outcomes of our multi-institutional report are in line with these results, with 2-year BFS, CRS, and CSS of 25%, 52%, and 92%, respectively. As with the aforementioned series, ~50% of our patients achieved complete BR after surgery, but the majority of our cohort developed BCR, with a mean time to BCR of 19 months. CRs were noted in a significant number of patients (40.5%), mainly at nodal or bone level. We do not know if these patients developed a true recurrence after sLND, or whether they already had more extensive systemic disease not detected by PET/CT. In this case, one might argue that these patients were not ideal candidates for surgery.

Several considerations, however, have to be made regarding the benefits of metastasis-directed surgery, at least for a sub-group of our patients. Among our cohort, 30% of patients remained with undetectable PSA after 2 years, and 60% were free from CR. Cancer-specific mortality was <5%. Another beneficial outcome of sLND is HRT-free survival: HRT can be avoided in these patients, or avoided for some time, sparing them from the side-effects of this treatment[13] and possibly delaying the time to CRPC.[14] Due to the retrospective design of our study, it was not possible to retrieve all data concerning the length and type of HRT administered to our patients. However, we observed that 71 of our patients (66.9%) received some form of HRT postoperatively, the duration of which was physician-driven but usually brief. The remaining 33.1% of cases remained HRT-free after sLND.[11]

When planning a sLND, the morbidity of this surgery must be taken into account. Most of the reported complications in the literature appear to be mild, the most frequent ones being lymphorrhoea (15.3%), fever (14.5%), and ileus (11.2%). The need for postoperative intervention due to severe complications was only sporadically reported.[6,10,15,16] Our data confirm that most postoperative complications are mild and self-limiting. However, around 10% of our patients experienced severe complications such as haemorrhage, hydronephrosis, or rectovesical fistulae, reminding us of the morbidity of this surgery. Again, accurate selection of patients is essential in order to ensure that the benefits of surgery outweigh the risks.

In an attempt to improve the selection of patients suitable for sLND, several authors have proposed factors that may help to identify the most-suited candidates.[6] Rigatti et al.[15] showed that pre-sLND PSA >4 ng/mL and the presence of retroperitoneal uptake at PET/CT represented independent preoperative predictors of CR, whereas the presence of pathologic nodes in the retroperitoneum, higher number of positive nodes, and complete BR after sLND represented postoperative independent predictors of CR.[15] Additionally, Jilg et al.[16] defined a Gleason score of 8–10 as an independent predictor of clinical progression. On the other hand, Karnes et al.[10] were not able to find any significant prognostic variable for systemic progression or CSS, likely as a result of the short follow-up or the heterogeneity of their cohort.

The results of our study are noteworthy, as CPRC status, PSA at time of sLND, and biochemical failure after sLND were all significant predictors of CR, both at univariable and multivariable analyses. According to our results, patients with CPRC status or high PSA values at the time of sLND may not be ideal candidates for metastasis-directed surgery. Surprisingly, the number of positive nodes at sLND was not associated with CR. The guidance of PET/CT is essential to select patients for sLND. The accuracy and limitations of $^{11}$C-choline PET/CT in this setting have been discussed elsewhere;[8] however, the diagnostic reliability of $^{11}$C-choline PET/CT seems to improve in the case of fast-PSA kinetics or increasing levels of PSA.[20]

Our study shares the limitations of previous reports, with its retrospective design and a median follow-up of 22.5 months. The heterogeneity of our cohort in terms of patient characteristics at sLND, surgical template, and postoperative management, limits the validity of our observations. The lack of a control group prevented us from reliably assessing the efficacy of surgery compared to traditional HRT. Hopefully, the results of an ongoing randomised, Phase II trial comparing eradication of oligo-recurrent disease versus active surveillance and androgen deprivation therapy at clinical progression[21] will help to shed light on this issue.

## CONCLUSIONS

According to the results of this multicentric cohort, which is the largest sLND series published to date, sLND represents a valid treatment option for selected patients with nodal recurrences. However, patients with CPRC status or high PSA values may not be the best candidates for a sLND. The morbidity of sLND and the significant risk of clinical progression despite surgery must be kept in mind during patient counselling.

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